constant regions and V framework regions for human sequences and results in a significantly less immunogenic product (Harding et al. (2010), MAbs. 2010 May-Jun; 2(3): 256–265).

However, it is known and also turned out in connection with the attempt of humanizing TH69 mAb that it is challenging to obtain a humanized version of a monoclonal murine antibody which fully retains the high affinity in the nanomolar range and the thermal stability of the mouse TH69 antibody. Importantly, it was found to be challenging to obtain humanized version of TH69 with no unfavorable characteristics or even favorable characteristics. This challenging task is solved by the antibody of the present invention.

Summary

Accordingly the present disclosure relates in a first aspect to an antibody binding to CD7, wherein the antibody comprises the V_H region determined by the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence being at least 90%, preferably at least 95% identical thereto; and the V_L region determined by the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence being at least 90%, preferably at least 95% identical thereto, provided that the three CDRs of the V_H region are determined by the amino acid sequences of SEQ ID NOs 3 to 5, and the three CDRs of the V_L region are determined by the amino acid sequences of SEQ ID NOs 6 to 8 (SEQ ID NO: 7 “AAS”).

The term “antibody” as used in accordance with the present disclosure comprises, for example, polyclonal or monoclonal antibodies. Furthermore, also derivatives or fragments thereof, which still retain the binding specificity to the target are comprised in the term "antibody". Antibody fragments (in particular (antigen) binding fragments) or derivatives comprise, inter alia, Fab or Fab’ fragments, Fd, F(ab')2, Fv or scFv fragments, single domain VH or V-like domains, such as VHH or V-NAR-domains, as well as multimeric formats such as minibodies, diabodies, tribodies or triplebodies, tetrabodies or chemically conjugated Fab’-multimers (see, for example, Harlow and Lane "Antibodies, A Laboratory Manual", Cold Spring Harbor Laboratory Press, 198; Harlow and Lane “Using Antibodies: A Laboratory Manual” Cold Spring Harbor Laboratory Press, 1999; Altshuler EP, Serebryanaya DV, Katrukha AG. 2010, Biochemistry (Mosc)., vol. 75(13), 1584; Holliger P, Hudson PJ. 2005, Nat Biotechnol., vol. 23(9), 1126). The multimeric formats in particular comprise bispecific antibodies that can simultaneously bind to two different types of antigens and trispecific antibodies that can simultaneously bind to three different types of antigens. The first antigen can be found on the protein in accordance with the disclosure. A second and/or third antigen may, for example, be a tumor marker that is specifically expressed on cancer cells or a certain type of cancer cells. Non-limiting examples of bispecific antibodies formats are Biclonics (bispecific, full length human IgG antibodies), DART (Dual-affinity Re-targeting Antibody), DuoBodies (Genmab) and BiTE (consisting of two single-chain variable fragments (scFvs) of different antibodies) molecules (Kontermann and Brinkmann (2015), Drug Discovery Today, 20(7):838-847). The antibody to be coupled to the antibody of the disclosure is generally distinct from the antibody of the disclosure. By the second antibody a second binding specificity to an antigen other than CD7 can be coupled to the CD7 antibody of the disclosure, thereby generating a bispecific construct.

The term “antibody” also encompasses an antibody or binding fragment thereof being fused to Fc parts (thereby generating a Fc fusion protein). The coupling of an Fc part of an antibody to the antibody of the disclosure is a further means for extending the *in vivo* half-life of the antibody of the disclosure.

The term "antibody" according to the disclosure is a humanized antibody; i.e. a human antibody with the exception of non-human CDRs of the antibody.

Various techniques for the production of antibodies are well known in the art. Examples for such techniques are described, e.g. in Harlow E and Lane D, Cold Spring Harbor Laboratory Press, 1988; Harlow E and Lane D, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1999. The parent TH69 mAb is a murine antibody that was prepared by immunizing mice with CD7-positive T-ALL cells. Furthermore, recombinant antibodies may be obtained from monoclonal antibodies or can be prepared *de novo* using various display methods such as phage, ribosomal, mRNA, or cell display. A suitable system for the expression of the recombinant (humanized) antibodies may be selected from, for example, bacteria, yeast, insects, mammalian cell lines or transgenic animals or plants (see, e.g., US patent 6,080,560; Holliger P, Hudson PJ. 2005, Nat Biotechnol., vol. 23(9), 11265). Further, techniques described for the production of single chain antibodies (see, inter alia, US Patent 4,946,778) can be adapted to produce single chain antibodies specific for an epitope of CD7. Surface plasmon resonance as employed in the BIAcore system can be used to measure the affinity of antibodies.

CD7 (Cluster of Differentiation 7) is a protein that in humans is encoded by the CD7 gene. The CD7 antigen is a cell surface glycoprotein found on thymocytes and mature T cells. It is one of the earliest antigens to appear on the surface of cells of the T-lymphocyte lineage and the most reliable clinical marker of T-cell acute lymphocytic leukemia. CD7 is an attractive therapeutic target for T-lymphoblastic leukemia/lymphoma (T-ALL/LBL).

The antibody of the disclosure specifically binds to CD7.

The amino acid sequences of SEQ ID NOs 3 and 4 are identical to the first and second CDRs of the V_H region of the murine monoclonal antibody TH69. The amino acid sequence of SEQ ID NO 5 is similar to the third CDR of the V_H region of the murine monoclonal antibody TH69 with one amino acid exchange in position 2. SEQ ID NOs 6 to 8 (SEQ ID NO: 7 “AAS”) are the three CDRs of the fully-human V_L region and not derived from the murine monoclonal antibody TH69. The corresponding nucleotide sequences of the six CDRs are shown in SEQ ID NOs 11 to 16 (SEQ ID NO: 15: GCTGCATCC).

The amino acid sequences of SEQ ID NOs 1 and 2 are the V_H region and the V_L region of the exemplified humanized TH69 antibody (huTH69; see examples section herein below) and the corresponding nucleotide sequences are SEQ ID NOs 9 and 10.

In accordance with the first aspect of the disclosure also amino acid sequences being at least 90%, preferably at least 95% identical to SEQ ID NO: 1 and SEQ ID NO: 2 are envisioned, provided that the six CDRs of SEQ ID NOs 3 to 8 (SEQ ID NO: 7 “AAS”) remain unchanged. Since such amino acid sequences retain a high sequence identity with SEQ ID NO: 1 and SEQ ID NO: 2, it can safely be assumed that such antibodies retain the favorable properties of huTH69 that will be discussed herein below.

In accordance with the present disclosure, the term “percent (%) sequence identity” describes the number of matches (“hits”) of identical nucleotides/amino acids of two or more aligned nucleic acid or amino acid sequences as compared to the number of nucleotides or amino acid residues making up the overall length of the template nucleic acid or amino acid sequences. In other terms, using an alignment for two or more sequences or subsequences the percentage of amino acid residues or nucleotides that are the same (e.g. 90% or 95% identity) may be determined, when the (sub)sequences are compared and aligned for maximum correspondence over a window of comparison, or over a designated region as measured using a sequence comparison algorithm as known in the art, or when manually aligned and visually inspected. This definition also applies to the complement of any sequence to be aligned.

Nucleotide and amino acid sequence analysis and alignment in connection with the present disclosure are preferably carried out using the NCBI BLAST algorithm (Stephen F. Altschul, Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), Nucleic Acids Res. 25:3389-3402). BLAST can be used for nucleotide sequences (nucleotide BLAST) and amino acid sequences (protein BLAST). The skilled person is aware of additional suitable programs to align nucleic acid and amino acid sequences.

The antibody of the disclosure binds CD7 with increased preference with a K_D of 200 nM or lower, 100 nM or lower, 50 nM or lower, 10 nM or lower, 5 nM or lower and 2 nM or lower. It is known in the art that the specific K_D value also depends on the particular antibody format; e.g. Fab or full-length antibody; see examples herein below.

The term "K_D" refers to the equilibrium dissociation constant (the reciprocal of the equilibrium binding or affinity constant) and is used herein according to the definitions provided in the art.

The K_D value with which the antibody of the disclosure binds CD7 can be determined by well-known methods including, without being limiting, surface plasmon resonance (SPR) spectroscopy, fluorescence titration, competition ELISA, calorimetric methods, such as isothermal titration calorimetry (ITC), flow cytometric titration analysis (FC titration), radioligand binding assays and surface plasmon resonance spectroscopy (BIAcore). Such methods are well known in the art and have been described e.g. in De Jong, L.A.A. et al. [2005] J. Chromatogr. B 829(1–2):1-25; Heinrich, L. et al. [2010] J. Immunol. Methods 352(1-2):13-22.

Preferably, surface plasmon resonance (SPR) spectroscopy is employed to determine the K_D. Even more preferably, the K_D is determined by ELISA. The use of SPR spectroscopy is illustrated by the appended examples (see section “Surface plasmon resonance spectroscopy”) and the SPR spectroscopy is preferably carried out as in the examples.

The antibody (huTH69-DE) of the disclosure displays with increased preference a thermal stability as a purified protein of at least 40°C, at least 45°C, at least 47.5°C, and at least 50°C, and at least 50.3°C. The antibody (huTH69-wt) of the disclosure displays with increased preference a thermal stability as a purified protein of at least 60°C, at least 65°C, at least 70°C., at least 72°C, and at least 72.3°C. The thermal stability is preferably determined by a thermal shift assay.

The use of a thermal shift assay is illustrated by the appended examples (see section “Thermal shift assay”) and the thermal shift assay is preferably carried out as in the examples.

A humanized version of the murine CD7 antibody TH69 (mTH69) was generated by combining CDR-grafting of the VH in a human framework and guided selection of a fully-human VL by phage display. The humanized TH69 (huTH69) retains a high affinity in the nanomolar range comparable to the chimeric TH69 (chimTH69) with fully-mouse V regions and an equilibrium dissociation constant (K_D) of 1.79 nM analyzed by surface plasmon resonance (SPR) spectroscopy as shown in the appended examples. The huTH69 showed a thermal stability comparable to the chimTH69 antibody and clinical approved antibodies such as cetuximab. It displays a melting temperature of 50.3°C as determined by a thermal shift assay for the huTH69 with a DE-modification in the Fc part (huTH69-DE) and a melting temperature of 72.3°C for huTH69 without the DE-modification (huTH69-wt). It is of note that the DE-modification in the Fc part (huTH69-DE vs. huTH69-wt) lowers melting temperatures (Amersdorffer J., et al., U.S. Patent 20140227277. 2012.). Importantly, no unfavorable biochemical and biophysical properties potentially negatively impacting its ability for clinical development were found in the variable regions of the humanized antibody (e.g., unpaired cysteines, N-glycosylation sites, asparagine deamidation, aspartate isomerization).

As outlined in the appended examples, the humanized version (huTH69) of the murine CD7 antibody TH69 (TH69 or mTH69) was generated by combining CDR-grafting of the VH in a human framework and guided selection of a fully-human VL by phage display from a human κ light-chain library. The described unique candidate huTH69 is the result of a complex and inventive selection process in terms of the chosen humanization strategy and the used screening process. It was in particular difficult to obtain the light chain of huTH69. The attempt to obtain a humanized light chain of TH69 via CDR-grafting failed. As an alternative approach for the humanization of the light chain a fully-human VL using guided-selection was carried out. A scFv-antibody library was generated from the CDR-grafted humanized VH of TH69 and the VL fragments (κ and λ light chains) were amplified from the RNA of B cells from eight healthy human donors. The huTH69 light chain was isolated from a pool of candidates (1 $x10^8$ κ light chains and 1 $x10^8$ λ light chains) by phage display performing two rounds of screening (panning) on the CD7-positive cell line CEM. Finally, only one CD7-specific light chain was enriched by phage display

out of 1 x10^8 κ light chains and 1 x10^8 λ light chains. As explained, only this huTH69 antibody, with humanized CDR-grafted heavy chain and the fully-human light chain, showed the same CD7 binding specificity as TH69.

In accordance with a preferred example of the first aspect of the disclosure the antibody comprises a V_H region differing by no more than 5, preferably by no more than 3 amino acid substitutions from SEQ ID NO: 1 and most preferably V_H region comprising SEQ ID NO: 1, and/or a V_L region differing by no more than 5, preferably by no more than 3 amino acid substitutions from SEQ ID NO: 2 and most preferably V_L region comprising SEQ ID NO: 2.

In accordance with this preferred example the framework regions within the V_H region and the V_L region of SEQ ID NO: 1 and SEQ ID NO: 2 may only differ from the exact sequences of SEQ ID NO.1 and SEQ ID NO: 2, each independently by no more than 5 and preferably by no more than 3 amino acid substitutions. The no more than 3 amino acid substitutions are preferably 2 amino acid substitutions and most preferably 1 amino acid substitution.

Since the antibody of this preferred example only allows for very few amino acid replacements as compared to SEQ ID NO: 1 and SEQ ID NO: 2, it can safely be assumed that such antibodies retain the above-discussed favorable properties of huTH69.

In accordance with a more preferred example of the first aspect of the disclosure the amino acid substitutions are conservative amino acid substitutions.

It is well known that particular conservative amino acid substitutions in the framework regions of an antibody essentially do not affect the properties of the antibody.

The term “conservative amino acid substitution” designates the replacement of an amino acid by another amino acid having a side chain with similar biochemical properties. The naturally occurring amino acids can be classified as shown in the following table:

Class	**Amino acids**	**1-letter code**
Aliphatic	Alanine, Valine, Leucine, Isoleucine	A, V, L, I
S/Se-containing	Cysteine, Selenocysteine, Methionine	C, U, M
Cyclic	Proline	P
Non-chiral	Glycine	G
Aromatic	Phenylalanine, Tyrosine, Tryptophan	F, Y, W
Basic	Histidine, Lysine, Arginine	H, K, R
Acidic	Aspartate, Glutamate,	D, E
Hydrophilic	Serine, Threonine, Asparagine, Glutamine	S, T, N, Q

It is preferred that a conservative amino acid substitution is the replacement of (i) an aliphatic amino acid (G, A, V, L, I) by another aliphatic amino acid, (ii) a S/Se-containing amino acid (C, U, M) by another S/Se-containing amino acid, (iii) an aromatic amino acid (F, Y, W) by another aromatic amino acid, (iv) a basic amino acid (H, K, R) by another basic amino acid, (v) an acidic amino acid (D, E) by another acidic amino acid, or (vi) a hydrophilic amino acid (S, T, N, Q) by another hydrophilic amino acid.

In accordance with a further preferred example of the first aspect of the disclosure CD7 is determined by the amino acid sequence of SEQ ID NO: 17.

SEQ ID NO: 17 shows the amino acid sequence of the human CD7 protein. The human CD7-positive T-ALL cell line (HSB-2) was used to generate and characterize the mTH69. Recombinant purified CD7-Fc fusion protein was used for surface plasmon resonance (SPR) spectroscopy to characterize chimTH69 and huTH69 antibodies.

In accordance with another preferred example of the first aspect of the disclosure, the antibody comprises an Fc domain of SEQ ID NO: 18.

As discussed herein above, huTH69 was also produced with a variant Fc part carrying the so-called DE-modification (huTH69-DE). The DE-modification is known to improve Fc-mediated effector functions by enhancing FcγR binding and refers to the amino acid exchanges S239D and I332E in the CH2 domain of the Fc part. SEQ ID NO: 18 is census sequence taking into account the unmodified Fc domain and the exchanges S239D and/or I332E. All four options covered by SEQ ID NO: 18 are suitable Fc domains unmodified Fc domain, Fc domain with S239D, Fc domain with I332E and Fc domain with S239D and I332E, wherein the first and the last option are preferred and the last option is most preferred.

The data in the appended examples show that huTH69 potently triggered antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These Fcγ receptor (FcγR)-mediated effector functions were successfully enhanced by amino acid exchanges S239D and I332E in the CH2 domain of the Fc part.

Furthermore, the data in the appended examples show that huTH69 as wildtype IgG1 unexpectedly triggers complement dependent cytotoxicity more efficiently than the parental chimTH69 antibody and selected published humanized CD7 antibodies (Heinrich G, et al. J Immunol. 1989 Dec 1;143(11):3589-97, WO 2022/095803, WO 2020/212710 and WO 2022/257835). huTH69 was especially more active when target cells expressed lower levels of the CD7 antigen.

In accordance with a further preferred example of the first aspect of the disclosure, the antibody is coupled to (a) a labelling group, (b) a toxin, (c) a drug, (d) a radionucleotide, (e) a cytokine, (f) a chemokine, (g) an enzyme, (h) a component modulating serum half-life, (i) an antibody or an Fc part thereof, or (j) an antibody mimetic.

The labelling group is a group that allows the detection of the antibody, preferably *in vivo* in a subject. The labelling group is preferably a fluorescent dye. The fluorescent dye is preferably a component selected from Alexa Fluor dyes, (BODIPY) dye, Cy dyes, Dy dyes, IRDye dyes, HiLyte Fluor dyes, Oregon dyes, TRITC, Rhodamine, and Fluorescein. and derivatives thereof including, but not limited to, NHS esters, maleimides, phosphines, and free acids. Non-limiting further examples of fluorescent proteins are green fluorescent protein (GFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), cyan fluorescent protein (CFP) and infrared fluorescent protein (IFP). The labelling group is also preferably a contrast agent. A contrast agent as used herein is a substance used to enhance the contrast of structures or fluids within the body in medical imaging. Common contrast agents work based on X-ray attenuation or magnetic resonance signal enhancement.

The antibody of the disclosure can be used for photodynamic therapy by the attachment of suitable photosensitizing functional group comprising, but not limited to, porphyrins, chlorins, bacteriochlorins, phthalocyanines (e.g., IR700DX), phenothiazinium salts, benzophenothiazinium salts, squaraine, phenalenone, BODIPY dyes, ruthenium, rhodium, and iridium complexes, hypericin, flavins, and genetically encoded proteins such as KillerRed protein.

The toxin is preferably a small organic compound or a polypeptide, more preferably a toxic compound selected from the group consisting of, but not limited to, calicheamicin, maytansinoid, neocarzinostatin, esperamicin, dynemicin, kedarcidin, maduropeptin, doxorubicin, daunorubicin, auristatin, Ricin-A chain, modeccin, truncated Pseudomonas exotoxin A, diphtheria toxin and gelonin.

The drug is a compound that is capable to treat or prevent a disease. The disease is preferably a tumor and most preferably T-lymphoblastic leukemia/lymphoma (T-ALL/LBL). As discussed above, CD7 is a therapeutic target for tumor treatment. CD7 could also be a target for clinical settings in which T cells (or NK cells) contribute to the pathogenic manifestation e.g graft versus host disease (GVHD).

The radionuclide is preferably either selected from the group of gamma-emitting isotopes, more preferably ^{99m}Tc, ^{123}I, ^{125}I, or ^{111}In, and/or from the group of positron emitters, more preferably ^{18}F, ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{89}Zr, or ^{124}I, and/or from the group of beta-emitters, more preferably ^{131}I, ^{90}Y, ^{177}Lu, or ^{67}Cu, and/or from the group of alpha-emitters, preferably ^{213}Bi, ^{212}Bi, ^{227}Th, ^{212}Ph, ^{223}Ra, ^{225}Ac, or ^{211}At. The radionuclide is more preferably a positron emitter since they are particularly suitable for diagnostics, e.g. via positron emission tomography imaging or single-photon emission computed tomography (SPECT). For therapeutic applications the radionuclide is more preferably an alpha-emitter or a beta-emitter.

The cytokine is preferably selected from the group consisting of IL-2, IL-12, TNF-alpha, IFN alpha, IFN beta, IFN gamma, IL-10, IL-15, IL-24, GM-CSF, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-13, IL-18, IL21, LIF, CD80, B70, TNF beta, LT-beta, CD-40 ligand, Fas-ligand, TGF-beta, IL-1alpha and IL-1beta. As it is well known in the art, cytokines may favor a pro-inflammatory or an anti-inflammatory response of the

immune system. Thus, depending on the disease to be treated either fusion constructs with a pro-inflammatory or an anti-inflammatory cytokine may be favored. For example, for the treatment of cancer, in particular prostate cancer in general fusion constructs comprising pro-inflammatory cytokines are preferred. Anti-inflammatory cytokines may be used, for example, to avoid autoimmune reactions.

The chemokine is preferably selected from the group consisting of IL-8, GRO alpha, GRO beta, GRO gamma, ENA-78, LDGF-PBP, GCP-2, PF4, Mig, IP-10, SDF-1alpha/beta, BUNZO/STRC33, I-TAC, BLC/BCA-1, MIP-1alpha, MIP-1 beta, MDC, TECK, TARC, RANTES, HCC-1, HCC-4, DC-CK1, MIP-3 alpha, MIP-3 beta, MCP-1-5, eotaxin, Eotaxin-2, I-309, MPIF-1, 6Ckine, CTACK, MEC, lymphotactin and fractalkine.

An enzyme is a protein that catalyzes a particular chemical or biochemical reaction. Antibody-enzyme fusion proteins have been used, for example, to target tumors for cancer therapy in two ways. In one system, an antibody-enzyme is pretargeted to the tumor followed by administration of an inactive prodrug that is converted to its active form by the pretargeted enzyme. This system has been described as antibody-directed enzyme prodrug therapy (ADEPT). Suitable enzymes for prodrug activation will be further discussed herein below in the section on enzymes. The other system uses antibody-enzyme fusion proteins as direct therapeutics, where the enzyme is toxic by itself. The key feature in this approach is that the antibody is used to target and subsequently internalize the toxic enzyme into the tumor cell, which activates cell-death processes. This antibody-enzyme system has been largely applied to deliver ribonucleases.

Enzymes may also be used for imaging in diagnostics. Conjugation partners in this regard include enzymes capable of catalyzing chromogenic, chemiluminescent or fluorescent reactions, such as e.g. horseradish peroxidase (HRP), luciferase, alpha-galactosidase and alkaline phosphatase (AP). For example, the conjugation partner can also be an enzyme capable of liberating or activating cytotoxic agents that have been brought into the vicinity of the targeted tissue, for example an enzyme for prodrug activation, such as e.g. an enzyme selected from the group consisting of carboxypeptidases, glucuronidases and glucosidases (Bagshawe, K.D. [2009] Curr. Drug Targets 10:152-157; Chen, K.-C. [2011] Bioconjugate Chem. 22:938–948). For certain applications a truncated version of an enzyme is preferred, for example by omitting a binding domain, provided that the truncated version retains or essentially retains the enzymatic activity of the full-length enzyme. Thus, with respect to the truncated version of the enzyme it is to be understood that they retain or essentially retain the enzymatic activity of the full-length enzyme.

Several compounds are available to extend the half-life of therapeutics, including antibodies. Two of the most common and preferred options are PEGylation and fusion with human serum albumin. Other options are the chemical coupling of polymers and carbohydrates, post-translational modifications such as N -glycosylation, and fusion to recombinant polymer mimetics.

In accordance with a more preferred example of the first aspect of the disclosure the antibody mimetic is selected from affibodies, adnectins, anticalins, DARPins, avimers, nanofitins, affilins, Kunitz domain peptides, Fynomers®, and trispecific binding molecules and probodies.

As used herein, the term “antibody mimetics” refers to compounds or proteins which, like antibodies, can specifically bind antigens, but which are not structurally related to antibodies. Antibody mimetics are usually artificial peptides or proteins with a molar mass of about 3 to 30 kDa. The antibody mimetic is preferably selected from the group consisting of an Anticalin, Affibody, Adnectin, DARPin, Avimer, Nanofitin, Affilin, β-Wrapin, ADAPT, Monobody, RasIn, FingR, Pronectin, Centyrin, Affilin, Affimer, Adhiron, Affitin, αRep, Repebody, i-body, Fynomer or Kunitz domain protein.

Lipocalin-derived binding proteins, also referred to as anticalins, represent a class of non-immunoglobulin binding proteins based on the human lipocalin scaffold. Lipocalins comprise a diverse family of small (20 kDa) extracellular proteins that occur in many species ranging from bacteria to humans and serve for the transport or scavenging of physiological compounds. Despite mutually low sequence homology, the three-dimensional fold of lipocalins is highly conserved (Rothe and Skerra (2018), BioDrugs. 2018; 32(3): 233–243.). Anticalins constitute an emerging class of artificial binding proteins obtained by combinatorial design based on the compact and robust human lipocalin scaffold. Due to their human origin, anticalins have low immunogenic potential, and in several clinical trials anticalins with different target specificities have demonstrated safety. The lipocalin-derived binding protein is preferably a lipocalin 2 (Lcn2)-derived binding protein. Lipocalin-2 (Lcn2), also known as neutrophil gelatinase-associated lipocalin (NGAL), is a protein that in humans is encoded by the LCN2 gene. Human LCN2 mRNA is, for example, represented by the NCBI Reference Sequence: NM_005564.5 (as available on March 12, 2019) and the amino acid sequence of human Lcn2 protein including the signal peptide is, for example, represented by the UniProt ID P80188-2 (as available on November 1, 1995).

"Affibodies", in accordance with the present disclosure, are a family of antibody mimetics derived from the Z-domain of staphylococcal protein A. Affibodies are structurally based on a three-helix bundle domain. An affibody has a molecular mass of around 6 kDa and is stable at high temperatures and under acidic or alkaline conditions. Target specificity is obtained by randomization of amino acids located in two alpha-helices involved in the binding activity of the parent protein domain (Feldwisch, J & Tolmachev, V. [2012] Methods Mol. Biol. 899:103-126).

"Adnectins" and also “Monobodies”, in accordance with the present disclosure, are based on the 10th extracellular domain of human fibronectin III (10Fn3), which adopts an Ig-like sandwich fold with 2 to 3 exposed loops, but lacks the central disulphide bridge (Gebauer, M. & Skerra, A. [2009] Curr. Opin. Chem. Biol. 13:245-255 and Koide et al. 1998, J. Mol. Biol. 284:1141–51). Adnectins and Monobodies with the desired target specificity can be genetically engineered by introducing modifications into specific loops or other surface areas of the protein.

"DARPins", in accordance with the present disclosure, are designed ankyrin repeat domains that provide a rigid interface arising from typically three repeats corresponding to an artificial consensus sequence, whereby six positions per repeat are randomized. Consequently, DARPins lack structural flexibility (Gebauer, M. & Skerra, A. [2009] Curr. Opin. Chem. Biol. 13:245-255).

The term “Avimer”, as used herein, refers to a class of antibody mimetics which consist of two or more peptide sequences of 30 to 35 amino acids each, which are derived from A-domains of various membrane receptors and which are connected by linker peptides. Binding of target molecules occurs via the A-domain and domains with desired binding specificity can be selected, for example, by phage display techniques. The target specificity of the different A-domains contained in an avimer may, but do not have to be identical (Weidle UH, et al., (2013), Cancer Genomics Proteomics; 10(4):155-68).

“Nanofitins” and also an “Affitins” are antibody mimetic proteins that are derived from the DNA binding protein Sac7d of Sulfolobus acidocaldarius. Nanofitins and Affitins usually have a molecular weight of around 7kDa and are designed to specifically bind a target molecule by randomizing the amino acids on the binding surface (Mouratou B, Béhar G, Paillard-Laurance L, Colinet S, Pecorari F., (2012) Methods Mol Biol.; 805:315-31.

The term “Affilin”, as used herein, refers to antibody mimetics that are developed by using either gamma-B crystalline or ubiquitin as a scaffold and modifying amino acids on the surface of these proteins by random mutagenesis. Selection of affilins with the desired target specificity is effected, for example, by phage display or ribosome display techniques. Depending on the scaffold, affilins have a molecular weight of approximately 10 or 20kDa. As used herein, the term affilin also refers to di- or multimerized forms of affilins (Weidle UH, et al., (2013), Cancer Genomics Proteomics; 10(4):155-68).

As used herein, the term "β-Wrapins” designates affibody protein homodimers with a disulfide bond between the pair of Cys28 residues connecting the two identical monomer subunits, referred to as subunits 1 and 2. The scaffold used in engineering β-wrapins is $ZA\beta_3$, an Aβ-binding affibody protein that not only prohibits the initial aggregation of Aβ monomers into toxic forms, but also dissociates pre-formed oligomeric aggregates by sequestering and stabilizing a β-hairpin conformation of Aβ monomers (Orr et al. (2018), Computers & Chemical Engineering, 116(4):322-332).

As used herein, the term "ABD-Derived Affinity Proteins (ADAPT)” refers to a class of antibody mimetics that has been created using the albumin-binding domain (ABD) of streptococcal protein G as a stable protein scaffold (Garousi et al (2015), Cancer Res.; 75(20):4364-71). By diversifying a surface of the domain that is not directly involved in albumin binding, molecules can be selected to bind a novel target and still retain their ability to bind albumin. This strategy has been used to select binders to a number of proteins, for example, the cancer-related epidermal growth factor receptor 3.

As used herein “RasIns” are 10FnIII-based antibody mimetics. Hence, they use the 10th domain of human fibronectin as their scaffold. RasIns are disulfide-free intrabodies. They were shown to be stable

inside cells and also when fused with a fluorescent protein label (Cetin eat al. (2017), J Mol Biol.; 429(4):562–573).

As used herein, the term “FingRs (Fibronectin intrabodies generated with mRNA display)” designates recombinant antibody-like proteins also being based on the 10FnIII scaffold (Gross eat al. (2013), Neuron.; 78(6): 971–985.).

As used herein, the term “Pronectins” designates recombinant antibody-like proteins being based on the fourteenth type-III scaffold of human fibronectin (14Fn3). The well-characterized fibronectin protein is prevalent throughout the human body. Human fibronectin, an extracellular protein, is naturally abundant in human serum. Intelligent loop-diversity has been designed to closely mimic the natural human repertoire and avoid sequence immunogenicity. The intrinsic properties of a Pronectin align with the pharmacological properties needed to make it a successful drug, including high potency, specificity, stability, favorable small size, and high-yield production in *E. coli* and yeast (http://www.protelica.com/pronectin_tech.html).

As used herein, the term “Centyrins” designates recombinant antibody-like proteins being based on the consensus tenascin FN3 framework (Tencon) (Diem et al. (2014), Protein Eng., Des. and Sel. 27, 419–429). Centryins against different targets, e.g. human c-MET, rTNFα and mIL-17A, were generated.

As used herein, “Affimers” refer to small proteins that bind to target molecules with similar specificity and affinity to that of antibodies. These engineered non-antibody binding proteins are designed to mimic the molecular recognition characteristics of monoclonal antibodies in different applications. In addition, these affinity reagents have been optimized to increase their stability, make them tolerant to a range of temperatures and pH, reduce their size, and to increase their expression in *E. coli* and mammalian cells. Derived from the cysteine protease inhibitor family of cystatins, which function in nature as cysteine protease inhibitors, these 12–14 kDa proteins share the common tertiary structure of an α-helix lying on top of an anti-parallel β-sheet (Tiede et al. (2017), eLife.; 6: e24903).

The class of recombinant antibody-like proteins designated as “Adhirons” herein is based on a phytocystatin consensus sequence as the scaffold (Tiede et al. (2014) Protein Eng. Des. Sel. 27, 145-55).

The class of recombinant antibody-like proteins designated as “αRep” herein is derived from alpha-helicoidal HEAT-like repeat protein scaffolds. In more detail, the αRep proteins are derived from a natural family of modular proteins comprising alpha-helical repeats, related to HEAT repeats, named after Huntingtin, the elongation factor 3 (EF3), the protein phosphatase 2A (PP2A), and the yeast kinase TOR. The association of several HEAT repeats forms alpha-solenoids of various lengths, which are naturally found in a number of cellular proteins involved in intracellular transport and protein-protein interaction (Hadpech et al. (2017), Scientific Reports; 7:Article number16335).

As used herein, the term “Repebodies” designates recombinant antibody-like proteins which are composed of leucine-rich repeat (LRR) modules. In more detail, the binding scaffold of Repebodies is based on variable lymphocyte receptors, which are non-immunoglobulin antibodies composed of LRR modules in jawless vertebrates. A template scaffold was first constructed by joining consensus repeat modules between the N- and C-capping motifs of variable lymphocyte receptors. The N-terminal domain of the template scaffold was redesigned based on the internalin-B cap by analyzing the modular similarity between the respective repeat units using a computational approach (Lee at al. (2012), Proc Natl Acad Sci; 109(9): 3299-3304).

As used herein, the term “i-bodies” refers to recombinant antibody-like proteins built on the scaffold of a human protein and engineered with two loops that mimic the shape of shark antibodies. These loops are responsible for binding or interacting with a particular target (in circulation or on a cell) that is causing disease. The i-body is a human analogue of the antigen binding domain of the shark antibody, which combines the advantages of monoclonal antibodies (high target specificity and affinity) with the beneficial stability features of small molecules (https://www.ibodies.eu/).

As used herein, the term "Fynomer" refers to a non-immunoglobulin-derived binding polypeptide derived from the human Fyn SH3 domain. Fyn SH3-derived polypeptides are well-known in the art and have been described e.g. in Grabulovski et al. (2007) JBC, 282, p. 3196-3204, WO 2008/022759, Bertschinger et al (2007) Protein Eng Des Sel 20(2):57-68, Gebauer and Skerra (2009) Curr Opinion in Chemical Biology 13:245-255, or Schlatter et al. (2012), MAbs 4:4, 1-12).

A “Kunitz domain peptide” is derived from the Kunitz domain of a Kunitz-type protease inhibitor such as bovine pancreatic trypsin inhibitor (BPTI), amyloid precursor protein (APP) or tissue factor pathway inhibitor (TFPI). Kunitz domains have a molecular weight of approximately 6kDa and domains with the required target specificity can be selected by display techniques such as phage display (Weidle et al., (2013), Cancer Genomics Proteomics; 10(4):155-68).

In accordance with a more preferred example of the first aspect of the disclosure the drug is selected from erlotinib (TARCEVA; Genentech/OSI Pharm.), bortezomib (VELCADE; MilleniumPharm.), fulvestrant (FASLODEX; AstraZeneca), sutent (SU11248; Pfizer), letrozole (FEMARA; Novartis), imatinib mesylate (GLEEVEC; Novartis), PTK787/ZK 222584 (Novartis), oxaliplatin (Eloxatin; Sanofi), 5-fluorouracil (5-FU, leucovorin, rapamycin (Sirolimus, RAPAMUNE; Wyeth), lapatinib (TYKERB, GSK572016; GlaxoSmithKline), lonafarnib (SCH 66336), sorafenib (BAY43-9006; Bayer Labs.), gefitinib (IRESSA; AstraZeneca), AG1478, AG1571 (SU 5271; Sugen), alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimine and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially, bullatacin and bullatacinone); camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues);

cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrousureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g, calicheamycin, especially calicheamycin gamma1 I and calicheamycin omegaI1(see, e.g., Agnew, Chem Intl ed Engl., 33: 183-186 (1994)) and dynemicin, including dynemicin A; bisphosphonate such as clodronate; esperamicin, neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, antrmycin, azaserine, bleomycins, cactinomycin, carabicin, carninomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubucin, 6-diazo-5-oxo-L-norleucine, ADRLIMYCIN® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubucin, liposomal doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptomigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites such as 5-fluorouracil(5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, and thiguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals such as aminoglutethimide, mitotane, and trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ('Ara-C'); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N. J.) ABRAXANETM cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumber, I11.), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; gemcitabine; 6-thioguanine; mercaptopurine; platinum analogs such as cisplatin, carboplatin; vinblastine; platinum; etoposide, ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DFMO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, solvates and acids thereof.

The above more preferred example is directed to preferred antibody-drug conjugates (ADCs). ADCs are one of the fastest growing anticancer drugs. This approach comprises a mAb conjugated to the

cytotoxic payload via a chemical linker directed toward a target antigen expressed on the tumor cell surface, reducing systemic exposure and therefore toxicity. TH69 binds CD7 which directs the antibody into the tumor cells, wherein the drug can battle the tumor.

In accordance with a further more preferred example of the first aspect of the disclosure the toxin is selected from auristatin (preferably monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF), domains II and HI of Pseudomonas exotoxin A, diphtheria toxin, ricin A, pokeweed antiviral protein, human pancreatic RNAse, geldanamycin, maytansinoids, calicheamycin, daunomycin, doxorubicin, methotrexate, vindesine, SG2285, dolastatin, dolastatin analogue's auristatin, cryptophycin, camptothecin, rhizoxin derivatives, CC-1065, duocarmycin, enediyne antibiotics, esperamicin, epothilone, an amatoxin (such alpha-amanitin), deruxtecan, exatecan analogue's (including exatecan), a pyrrolobenzodiazepin (PBD) dimer and toxoids.

The principle of the antibody–toxin conjugates is similar to the ADCs. TH69 binds CD7 which directs the toxin into the tumor cells, whereby the toxin can exert the toxic effect in the tumor cells. The mechanistic proof of concept that huTH69 is capable to deliver a truncated version of Pseudomonas exotoxin A is described in the appended Example 5.

The present disclosure relates in a second aspect to a nucleic acid or a set of two nucleic acid molecules, wherein the nucleic acid molecule encoding the antibody as disclosed herein, and the set of two nucleic acid molecules, wherein the first nucleic acid molecule encodes the V_H region of the antibody as disclosed herein and the second nucleic acid molecule encodes the V_L region of the antibody as disclosed herein.

As far as the nucleic acid molecule(s) refer to an antibody being coupled to one of the compounds as defined in the above items (a) to (j) it is to be understood that these compounds can also be encoded by the nucleic acid molecule(s) as long as the compound is a proteinaceous compound.

The term "nucleic acid molecule" in accordance with the present disclosure includes DNA, such as cDNA or double or single stranded genomic DNA and RNA. In this regard, "DNA" (deoxyribonucleic acid) means any chain or sequence of the chemical building blocks adenine (A), guanine (G), cytosine (C) and thymine (T), called nucleotide bases, that are linked together on a deoxyribose sugar backbone. DNA can have one strand of nucleotide bases, or two complementary strands which may form a double helix structure. "RNA" (ribonucleic acid) means any chain or sequence of the chemical building blocks adenine (A), guanine (G), cytosine (C) and uracil (U), called nucleotide bases, that are linked together on a ribose sugar backbone. RNA typically has one strand of nucleotide bases, such as mRNA. Included are also single- and double-stranded hybrids molecules, i.e., DNA-DNA, DNA-RNA and RNA-RNA. The nucleic acid molecule may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, and internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoroamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.). Nucleic acid

molecules, in the following also referred as polynucleotides, may contain one or more additional covalently linked moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (e.g., acridine, psoralen, etc.), chelators (e.g., metals, radioactive metals, iron, oxidative metals, etc.), and alkylators. The polynucleotides may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Further included are nucleic acid mimicking molecules known in the art such as synthetic or semi-synthetic derivatives of DNA or RNA and mixed polymers. Such nucleic acid mimicking molecules or nucleic acid derivatives according to the disclosure include phosphorothioate nucleic acid, phosphoramidate nucleic acid, 2'-O-methoxyethyl ribonucleic acid, morpholino nucleic acid, hexitol nucleic acid (HNA), peptide nucleic acid (PNA) and locked nucleic acid (LNA) (see Braasch and Corey, Chem Biol 2001, 8: 1). LNA is an RNA derivative in which the ribose ring is constrained by a methylene linkage between the 2'-oxygen and the 4'-carbon. Also included are nucleic acids containing modified bases, for example thio-uracil, thio-guanine and fluoro-uracil. A nucleic acid molecule typically carries genetic information, including the information used by cellular machinery to make proteins and/or polypeptides. The nucleic acid molecule of the disclosure may comprise promoters, enhancers, response elements, signal sequences, polyadenylation sequences, introns, 5'- and 3'- non-coding regions, and the like.

The nucleic acid molecule according to the disclosure encodes the antibody of the disclosure. The antibody of the disclosure may also be encoded by a set of two nucleic acid molecules. This is because an antibody (a full-length antibody or fragments, such as scFv or Fab) comprises heavy and light chain sequences which, for example, upon expression in a cell, self-assemble into an antibody. The heavy and light chain sequences can be encoded by a set of two different nucleic acid molecules.

The present disclosure relates in a third aspect to a vector comprising the nucleic acid molecule as disclosed herein in an expressible form or a vector or a set of two vectors comprising the set of two nucleic acid molecules as disclosed herein in an expressible form.

The vector or set of two vectors can optionally also comprise nucleic acid molecule encoding a proteinaceous compound as defined in any one of items (a) to (j) in an expressible form.

The term "vector" in accordance with the disclosure means preferably a plasmid, cosmid, virus, bacteriophage or another vector used e.g. conventionally in genetic engineering which encoding the antibody of the disclosure in expressible from. For the same reasons as discussed in connection with the set of nucleic acid molecules of the disclosure, the antibody of the disclosure may also be encoded by a set of vectors, preferably by a set of two vectors.

The nucleic acid molecule(s) encoding the antibody of the disclosure may, for example, be inserted into several commercially available vectors. Non-limiting examples include prokaryotic plasmid vectors, such as of the pUC-series, pBluescript (Stratagene), the pET-series of expression vectors (Novagen) or pCRTOPO (Invitrogen) and vectors compatible with an expression in mammalian cells like pREP (Invitrogen), pcDNA3 (Invitrogen), pCEP4 (Invitrogen), pMC1neo (Stratagene), pXT1 (Stratagene),

pSG5 (Stratagene), EBO-pSV2neo, pBPV-1, pdBPVMMTneo, pRSVgpt, pRSVneo, pSV2-dhfr, pIZD35, pLXIN, pSIR (Clontech), pIRES-EGFP (Clontech), pEAK-10 (Edge Biosystems) pTriEx-Hygro (Novagen) and pCINeo (Promega). Examples for plasmid vectors suitable for Pichia pastoris comprise e.g. the plasmids pAO815, pPIC9K and pPIC3.5K (all Invitrogen).

The nucleic acid molecules inserted into the vector can e.g. be synthesized by standard methods or isolated from natural sources. Ligation of the coding sequences to transcriptional regulatory elements and/or to other amino acid encoding sequences can also be carried out using established methods. Transcriptional regulatory elements (parts of an expression cassette) ensuring expression in prokaryotes or eukaryotic cells are well known to those skilled in the art. These elements comprise regulatory sequences ensuring the initiation of transcription (e. g., translation initiation codon, promoters, such as naturally-associated or heterologous promoters and/or insulators; see above), internal ribosomal entry sites (IRES) (Owens, Proc. Natl. Acad. Sci. USA 98 (2001), 1471-1476) and optionally poly-A signals ensuring termination of transcription and stabilization of the transcript. Additional regulatory elements may include transcriptional as well as translational enhancers. Preferably, the polynucleotide(s) encoding the antibody of the disclosure is operatively linked to such expression control sequences allowing expression in prokaryotes or eukaryotic cells. The vector may further comprise nucleic acid sequences encoding secretion signals as further regulatory elements. Such sequences are well known to the person skilled in the art. Furthermore, depending on the expression system used, leader sequences capable of directing the expressed polypeptide to a cellular compartment may be added to the coding sequence of the polynucleotide of the disclosure. Such leader sequences are well known in the art.

Furthermore, it is preferred that the vector comprises a selectable marker. Examples of selectable markers include genes encoding resistance to neomycin, ampicillin, hygromycin, and kanamycin. Specifically designed vectors allow the shuttling of DNA between different hosts, such as bacteria-fungal cells or bacteria-animal cells (e. g. the Gateway system available at Invitrogen). An expression vector according to this disclosure is capable of directing the replication, and the expression, of the polynucleotide and an encoded peptide or a fusion protein of this disclosure. Apart from introduction via vectors such as phage vectors or viral vectors (e.g. adenoviral, retroviral), the nucleic acid molecules as described herein above may be designed for direct introduction or for introduction via liposomes into a cell. Additionally, baculoviral systems or systems based on vaccinia virus or Semliki Forest virus can be used as eukaryotic expression systems for the nucleic acid molecules of the disclosure.

The present disclosure relates in a fourth aspect to a host cell, comprising the nucleic acid molecule or set of two nucleic acid molecules as disclosed herein or the vector of the set of two vectors as disclosed herein, wherein the host cell is preferably an anti-tumor leucocyte and wherein the anti-tumor leucocyte is preferably a chimeric antigen receptor T-cell (CAR T-cell), T-cell-receptor-engineered T-cell (TCR T-cell), chimeric antigen receptor NK-cell (CAR NK-cell), NK cell receptor-engineered NK cell (NCR NK-cell), TCR/CAR hybrid T-cell, NCR/CAR hybrid NK-cells, tumor-infiltrating lymphocytes (TIL) or CAR macrophage.

The host cell is preferably a non-human host cell or human host cell.

The term "host cell" means any cell of any organism that is selected, modified, transformed, grown, or used or manipulated in any way, for the production of the antibody of the disclosure by the cell and optionally a proteinaceous compound as defined in any one of items (a) to (j). The host cell is therefore generally an *ex vivo* or *in vitro* cell and/or an isolated cell or may be part of a non-human transgenic animal.

The host cell of the disclosure is typically produced by introducing the nucleic acid molecule(s) or vector(s) of the disclosure into the host cell which upon its/their presence mediates the expression of the nucleic acid molecule(s) of the disclosure encoding the antibody of the disclosure. The host from which the host cell is derived or isolated may be any prokaryote or eukaryotic cell or organism, preferably with the exception of human embryonic stem cells that have been derived directly by destruction of a human embryo.

Suitable prokaryotes (bacteria) useful as hosts for the disclosure are, for example, those generally used for cloning and/or expression like *E. coli* (e.g., *E coli* strains BL21, HB101, DH5a, XL1 Blue, Y1090 and JM101), *Salmonella typhimurium, Serratia marcescens, Burkholderia glumae, Pseudomonas putida, Pseudomonas fluorescens, Pseudomonas stutzeri, Streptomyces lividans, Lactococcus lactis, Mycobacterium smegmatis, Streptomyces coelicolor* or *Bacillus subtilis*. Appropriate culture mediums and conditions for the above-described host cells are well known in the art.

A suitable eukaryotic host cell may be a vertebrate cell, an insect cell, a fungal/yeast cell, a nematode cell or a plant cell. The fungal/yeast cell may be a *Saccharomyces cerevisiae* cell, *Pichia pastoris* cell, *Kluyveromyces lactis* cell, or an *Aspergillus* cell. Preferred examples of a host cell to be genetically engineered with the nucleic acid molecule or the vector(s) of the disclosure is a cell of yeast, *E. coli* and/or a species of the genus *Bacillus* (e.g., *B. subtilis*). In one preferred example the host cell is a yeast cell (e.g. *S. cerevisiae, K. lactis,* or *P. pastoris*).

In a different preferred example the host cell is a mammalian host cell, such as a Chinese Hamster Ovary (CHO) cell, mouse myeloma lymphoblastoid, human embryonic kidney cell (HEK-293), human embryonic retinal cell (Crucell's Per.C6), or human amniocyte cell (Glycotope and CEVEC). These cells are frequently used in the art to produce recombinant proteins. CHO cells are the most commonly used mammalian host cells for industrial production of recombinant protein therapeutics for humans.

Anti-tumor leucocytes are also preferred as host cells since they are useful as therapeutic cells in particular in tumor immune cell therapies. Furthermore, the humanized variable regions as described herein may be used as basis for the development of different immunotherapeutic strategies, including CAR T / CAR NK cells / CAR macrophages.

An anti-tumor leucocyte (or an anti-tumor effector leucocyte) is a leucocyte capable of eliciting a cytolytic response that can cause tumor cell death. These leucocytes are specializing in and equipped for tumor cell elimination. The first category encompasses clonally expanded T lymphocytes expressing a unique T cell receptor (TCR) and recognizing tumor epitopes in the context of the major histocompatibility complex (MHC) molecules. These T cells, optionally together with B cells producing tumor-specific antibodies and dendritic cells (DC) processing and presenting tumor epitopes, can mediate an adaptive immunity against tumors. The second category of effector cells includes natural killer (NK) cells, NK-T cells, and macrophages (M). These cells are not restricted by the MHC molecules in their interactions with tumor targets, and they mediate innate immunity. Each type of effector cells, whether specific or nonspecific, contains subsets of cells at different stages of differentiation and activation. This means that each type of effector cell is potentially able to target tumor cells within a heterogeneous mix of cells with distinct functional capabilities, depending on their stage of differentiation, maturation, and/or activation (Holland, Frei; Cancer Medicine; 6th edition. chapter “Antitumor Effector Cells in Humans”). All the above-described types of anti-tumor leucocytes are applicable in accordance with the present disclosure.

The anti-tumor leucocytes as describe herein are preferably T-cells, NK cells or macrophages.

T-cells or T-lymphocytes can be distinguished from other lymphocytes by the presence of a T-cell receptor (TCR) on their cell surface. One of the functions of T-cells is mediating immune-mediated cell death, and it is carried out by two major subtypes: CD8+ "killer" and CD4+ "helper" T-cells. CD8+ T cells are cytotoxic which means that they are able to directly kill selected cells. These selected cells are in accordance with the disclosure tumor cells (such as cancer cells). CD4+ cells function as "helper cells". Unlike CD8+ killer T-cells, these CD4+ helper T-cells function by further activating memory B cells and cytotoxic T-cells, which leads to a larger immune response which is in accordance with the disclosure directed against tumor cells. The specific adaptive immune response regulated by the T-helper cell depends on its subtype, which is distinguished by the types of cytokines they secrete. The T-cells are preferably a CD8+ killer T-cells or a mixture of CD8+ killer and CD4+ helper T-cells.

A natural killer (NK) cell is a type of cytotoxic lymphocyte being critical to the innate immune system that belong to the rapidly expanding family of the innate lymphoid cells (ILC) and represent 5–20% of all circulating lymphocytes in humans. The role of NK cells in the innate immune system is analogous to that of cytotoxic T-cells in the vertebrate adaptive immune response. NK cells provide rapid responses to virus-infected cells and other intracellular pathogens acting at around 3 days after infection and respond to tumor formation. Typically, immune cells detect the major histocompatibility complex (MHC) presented on infected cell surfaces, triggering cytokine release, causing the death of the infected cell by lysis or apoptosis. NK cells are unique, however, as they have the ability to recognize and kill stressed cells in the absence of antibodies and MHC, allowing for a much faster immune reaction. They were named "natural killers" because they do not require activation to kill cells that are missing "self" markers of MHC class I. This role is especially important because harmful cells that are missing MHC I markers cannot be detected and destroyed by other immune cells, such as T-cells.

The anti-tumor leucocytes are also preferably chimeric antigen receptor T-cells (CAR T-cells), T-cell-receptor-engineered T-cells (TCR T-cells), chimeric antigen receptor NK-cells (CAR NK-cells), NK cell receptor-engineered NK cells (NCR NK-cells), TCR/CAR hybrid T-cells, NCR/CAR hybrid NK-cells, chimeric antigen receptor macrophages (CAR-macrophages) or tumor-infiltrating lymphocytes (TILs).

Chimeric antigen receptor (CAR) T-cells are T-cells that have been genetically engineered to produce a chimeric T cell receptor (CAR) for use in immunotherapy. The receptors are chimeric because they combine both antigen-binding and T-cell activating functions into a single receptor. CAR-T cell therapy uses T-cells engineered with CARs for tumor (such as cancer) therapy. The premise of CAR-T immunotherapy is to modify T-cells to recognize tumor cells in order to more effectively target and destroy them. In order to generate CAR T-cells, T-cells are harvested from a subject, genetically altered, and then infused into patients to attack a tumor in the subject. CAR T-cells can be both CD4+ and/or CD8+ cells. A 1-to-1 ratio of both cell types is preferred since it provides synergistic antitumor effects.

CAR T-cells are engineered to transfer arbitrary specificity onto an immune effector cell, like a T cell, which specifically eliminates antigen-bearing tumor cells. The CAR may comprise a scFv being derived from an antibody, a CD3ζ and a transmembrane domain (so-called first-generation CARs). In this way, the engineered CAR is able to recognize specific tumor-associated antigens. Therefore, the CAR has the ability to bind unprocessed tumor surface antigens without MHC processing while TCRs engage with both tumor intracellular and surface antigenic peptides embedded in MHC molecules.

In contrast, TCRs are α/β heterodimers that bind to the MHC-bound antigens. As discussed above, CARs recognize tumor antigen which leads to T-cell activation with different functions compared with TCRs. CAR-T cell therapy has certain disadvantages like off-tumor toxicities when targeting tumor-specific antigen. Compared with CARs, TCRs have several structural advantages in T cell-based therapy, such as more subunits in their receptor structure (ten subunits vs one subunit), more immunoreceptor tyrosine-based activation motif (ITAMs) (ten vs three), less dependence on antigens (one vs 100), and more co-stimulate receptors (CD3, CD4, CD28, etc.) (Zhao et al. (2021) Front. Immunol., | https://doi.org/10.3389/fimmu.2021.658753).

CAR NK-cells are distinguished from CAR T-cells in that the chimeric antigen receptor is introduced into NK cells instead of T-cells. Just as CAR T-cells, CAR-NK cells can be engineered to target diverse antigens, enhance proliferation and persistence *in vivo*, increase infiltration into solid tumors, overcome resistant tumor microenvironment, and ultimately achieve an effective anti-tumor response.

CAR macrophages are distinguished from CAR T- / CAR NK-cells in that the chimeric antigen receptor is introduced into macrophages. Just as CAR T-cells / CAR-NK CAR macrophages can be engineered to target diverse antigens and enhance persistence *in vivo*, increase infiltration into solid tumors, overcome resistant tumor microenvironment, and ultimately achieve an effective anti-tumor response.

Natural cytotoxicity receptors (NCR) NK cells are NK-cell that have been genetically engineered to express a NCR. The NCRs have been proposed to bind to many cellular ligands which are implicated in NK cell surveillance of tumor cells. Many of these interactions have been shown to evoke the cytotoxic and cytokine-secreting functions of NK cells. However, it is also possible that the NCRs regulate other anti-tumor pathways. NCRs and their ligands can be successfully targeted for tumor (such as cancer) immunotherapy. NCRs have been classically defined as activating receptors delivering potent signals to NK cells in order to lyse harmful cells and to produce inflammatory cytokines.

TCR/CAR hybrid T-cells are T-cells that have been genetically engineered to express a TCR and CAR. Similarly, NCR/CAR hybrid NK-cells are T-cells that have been genetically engineered to express a NCR and CAR.

Tumor-infiltrating lymphocytes (TILs) are white blood cells that have left the bloodstream and migrate towards a tumor. TILs are implicated in killing tumor cells. The presence of lymphocytes in tumors is often associated with better clinical outcomes.

The tumor-infiltrating lymphocytes are preferably tumor-infiltrating T-cells or tumor-infiltrating NK cells.

In adoptive T-cell transfer therapy, TILs are expanded *ex vivo* from surgically resected tumors that have been cut into small fragments or from single cell suspensions isolated from the tumor fragments. Multiple individual cultures are established, grown separately and assayed for specific tumor recognition. TILs are typically expanded over the course of a few weeks with a high dose of IL-2 in 24-well plates. Selected TIL lines that presented best tumor reactivity are then further expanded in a "rapid expansion protocol" (REP), which uses anti-CD3 activation for a typical period of two weeks. The final post-REP TIL is infused back into a patient in order to treat a tumor of the patient. This *applies mutatis mutandis* to adoptive NK-cell transfer with TILs.

In addition, the anti-tumor lymphocytes are preferably autologous anti-tumor lymphocytes.

In an anti-tumor therapy with autologous lymphocytes the lymphocytes are taken from a subject having a tumor and are genetically engineered (e.g. to produce CAR T-cells) and/or selected and/or expanded (e.g. to produce TILs) *ex vivo* and then transferred back into the same subject. These autologous therapies are subject-specific because the therapeutic cells are created from a subject's own cells.

The present disclosure also relates to a transgenic animal, preferably a non-human transgenic animal comprising the vector or the set of two vectors of the disclosure.

Transgenic animals can be used for the production of antibodies as is reviewed, for example, in Brüggemann (2014), Arch Immunol Ther Exp (Warsz). 2015; 63(2): 101–108. The transgenic animal is preferably a mammal other than human. The antibodies may also be produced such that the antibodies

can be obtained from the milk of transgenic mammals. The mammal is therefore preferably a goat, sheep or cow.

The present disclosure relates in a fifth aspect to a method for producing an antibody as disclosed herein, comprising (a) culturing the host as disclosed herein under conditions that allow synthesis of said antibody; and (b) recovering said antibody from said culture.

When in the following the term “antibody” is used in connection with the discussion of the various examples of the disclosure, it is to be understood that this optionally also includes the proteinaceous compound as defined in any one of items (a) to (j) and, where applicable, any non-proteinaceous compound as defined in any one of items (a) to (j).

The term “culturing” specifies the process by which host cells are grown under controlled conditions. These conditions may vary dependent on the host cell used. The skilled person is well-aware of methods for establishing optimized culturing conditions. Moreover, methods for establishing, maintaining and manipulating a cell culture have been extensively described in the state of the art.

Methods of isolation of the antibody of the disclosure are well-known in the art and comprise without limitation method steps such as ion exchange chromatography, gel filtration chromatography (size exclusion chromatography), affinity chromatography, high pressure liquid chromatography (HPLC), reversed phase HPLC, disc gel electrophoresis or immunoprecipitation, see, for example, Antibody Purification Handbook, GE Healthcare, 18-1037-46.

The term “recovering said antibody from said culture” in accordance with the disclosure refers to the obtention of a product of a process implying that in the host cell a process can be induced by which information from nucleic acid molecule(s) encoding the antibody of the disclosure is/are used in the synthesis of the antibody of the disclosure. Several steps in this process may be modulated, including the transcription, RNA splicing, translation, and post-translational modification of the antibody of the disclosure by methods know in the art. Accordingly, such modulation may allow for control of the timing, location, and amount of antibody produced.

The present disclosure relates in another example to a diagnostic composition or a pharmaceutical composition comprising the antibody, the nucleic acid molecule or set of two nucleic acid molecules, the vector or set of two vectors or the host cell of the disclosure (or combination thereof). In a sixth aspect, the present disclosure relates to a diagnostic composition or a pharmaceutical composition comprising the antibody as disclosed herein, the nucleic acid molecule or set of two nucleic acid molecules as disclosed herein, the vector or set of two vectors as disclosed herein or the host cell as disclosed herein.

In accordance with the present disclosure, the term “pharmaceutical composition” relates to compositions for administration to a subject, preferably a human subject. In connection with the pharmaceutical composition the subject may be a patient, i.e. subject having a disease. In accordance with the present disclosure, also a ”diagnostic composition” relates to a composition for administration to a subject, preferably a human subject. A ”diagnostic composition” may furthermore relate to a composition to be contacted *in vitro* or *ex vivo* with a sample from a subject, preferably a human subject.

The diagnostic or pharmaceutical composition of the disclosure comprises the compounds recited above. It may, optionally, comprise further molecules capable of altering the characteristics of the compounds of the disclosure thereby, for example, stabilizing, modulating and/or activating their function. The composition may be in solid or liquid form or any other appropriate form and may be, *inter alia*, in the form of (a) powder(s), (a) tablet(s), (a) solution(s) or (an) aerosol(s). The composition may, optionally and additionally, comprise a pharmaceutically acceptable carrier. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions, organic solvents including DMSO etc. Compositions comprising such carriers can be formulated by well-known conventional methods.

While the diagnostic composition is to diagnose a disease within a subject or *ex vivo* or *in vitro* based on a sample from the subject (and in this regard, e.g. the presence, location and /or severity of the disease) the pharmaceutical composition is to treat or prevent the development of a disease in a subject.

The pharmaceutical compositions can be administered to the subject at a suitable dose in order to achieve a curative or disease preventive effect. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. The therapeutically effective amount for a given situation will readily be determined by routine experimentation and is within the skills and judgement of the ordinary clinician or physician. Generally, the regimen as a regular administration of the pharmaceutical composition should be in the range of 1 to 50 mg antibody / kg bodyweight every 1, 2, 3 or 4 weeks. However, a more preferred dosage might be in the range of 2 to 25 mg/kg every 1, 2, 3 or 4 weeks, even more preferably 3 to 20 mg/kg every 1, 2, 3 or 4 weeks. The length of treatment needed to observe changes and the interval following treatment for responses to occur vary depending on the desired effect. The particular amounts may be determined by conventional tests which are well known to the person skilled in the art.

The present disclosure relates in another example to the antibody, the nucleic acid molecule or set of two nucleic acid molecules, the vector or set of two vectors or the host cell of the disclosure for use in a method of treating, inhibiting or diagnosing *in vivo* a tumor, wherein the tumor is preferably a T-cell neoplasia, lymphoma or leukemia, and is most preferably a T-cell lymphoma or acute lymphocytic leukemia. In a seventh aspect, the present disclosure relates to a use of the antibody as disclosed herein, the nucleic acid molecule or set of two nucleic acid molecules as disclosed herein, the vector or set of two vectors as disclosed herein or the host cell as disclosed herein in the manufacture of a medicament for treating, inhibiting or diagnosing *in vivo* a tumor, wherein the tumor is preferably a T-cell neoplasia, lymphoma or leukemia, and is most preferably a T-cell lymphoma or acute lymphocytic leukemia.

The tumor can be a benign or a malignant tumor and is preferably a malignant tumor. A malignant tumor is also referred to herein as cancer. The tumor is also preferably a solid tumor and the cancer preferably a solid cancer.

Alternatively, the tumor is preferably a T-cell neoplasia, lymphoma or leukemia, and is most preferably a T-cell lymphoma or acute lymphocytic leukemia. As discussed herein above targeting CD7 is in particular useful in the diagnosis and treatment of these kinds of tumors.

Regarding the examples characterized in this specification, in particular in the claims, it is intended that each example mentioned in a dependent claim is combined with each example of each claim (independent or dependent) said dependent claim depends from. For example, in case of an independent claim 1 reciting 3 alternatives A, B and C, a dependent claim 2 reciting 3 alternatives D, E and F and a claim 3 depending from claims 1 and 2 and reciting 3 alternatives G, H and I, it is to be understood that the specification unambiguously discloses examples corresponding to combinations A, D, G; A, D, H; A, D, I; A, E, G; A, E, H; A, E, I; A, F, G; A, F, H; A, F, I; B, D, G; B, D, H; B, D, I; B, E, G; B, E, H; B, E, I; B, F, G; B, F, H; B, F, I; C, D, G; C, D, H; C, D, I; C, E, G; C, E, H; C, E, I; C, F, G; C, F, H; C, F, I, unless specifically mentioned otherwise.

Similarly, and also in those cases where independent and/or dependent claims do not recite alternatives, it is understood that if dependent claims refer back to a plurality of preceding claims, any combination of subject-matter covered thereby is considered to be explicitly disclosed. For example, in case of an independent claim 1, a dependent claim 2 referring back to claim 1, and a dependent claim 3 referring back to both claims 2 and 1, it follows that the combination of the subject-matter of claims 3 and 1 is clearly and unambiguously disclosed as is the combination of the subject-matter of claims 3, 2 and 1. In case a further dependent claim 4 is present which refers to any one of claims 1 to 3, it follows that the combination of the subject-matter of claims 4 and 1, of claims 4, 2 and 1, of claims 4, 3 and 1, as well as of claims 4, 3, 2 and 1 is clearly and unambiguously disclosed.

The above considerations apply *mutatis mutandis* to all appended claims.

Brief Description of the Figures

The figures show.

Figure 1. Generation and identification of humanized TH69. (a) A scFv antibody library was generated from the VH of murine TH96 (mTH69), humanized by CDR-grafting, and the VL fragments amplified from the RNA of B cells from eight human donors. The humanized TH69 (huTH69) was isolated from the library by phage display performing two panning rounds on the CD7-positive cell line CEM. **(b)** VH and VL amino acid sequences of TH69 before (mVH/mVL;SEQ ID NO: 21 and 22) and after humanization (huVH/huVL; SEQ ID NO: 1 and 2) by CDR-grafting or guided selection, respectively. CDR are labelled according to IMGT (bold/line). Backmutations in VH indicated in red. CDR: complementary determining region, VH: variable domain of heavy chain, VL: variable domain of light chain.

Figure 2: The humanized scFv huTH69 specifically binds CD7 in cell ELISA. 1 x 10^6 CEM cells without (black) and with (grey) pre-incubation with the parental mTH69 and 1 x 10^6 CEM cells with CD7 knock-out (CD7-KO-CEM, white) were incubated with 1 x 10^{10} colony-forming-units (CFU) phages

CLAIMS

1. An antibody binding to CD7, wherein the antibody comprises
the V_H region determined by the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence being at least 90%, preferably at least 95% identical thereto; and
the V_L region determined by the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence being at least 90%, preferably at least 95% identical thereto,
provided that
the three CDRs of the V_H region are determined by the amino acid sequences of SEQ ID NOs 3 to 5, and
the three CDRs of the V_L region are determined by the amino acid sequences of SEQ ID NOs 6 to 8 (SEQ ID NO: 7 "AAS").

2. The antibody of claim 1, wherein the antibody comprises
a V_H region differing by no more than 5, preferably by no more than 3 amino acid substitutions from SEQ ID NO: 1 and most preferably V_H region comprising SEQ ID NO: 1, and/or
a V_L region differing by no more than 5, preferably by no more than 3 amino acid substitutions from SEQ ID NO: 2 and most preferably V_L region comprising SEQ ID NO: 2.

3. The antibody of claim 2, wherein the amino acid substitutions are conservative amino acid substitutions.

4. The antibody according to any one of claims 1 to 3, wherein the CD7 is determined by the amino acid sequence of SEQ ID NO: 17.

5. The antibody according to any one of claims 1 to 4, wherein the antibody comprises an Fc domain of SEQ ID NO: 18.

6. The antibody according to any one of claims 1 to 5, wherein said antibody is coupled to
(a) a labelling group,
(b) a toxin,
(c) a drug,
(d) a radionucleotide,
(e) a cytokine,
(f) a chemokine,
(g) an enzyme,
(h) a component modulating serum half-life,
(i) an antibody, or
(j) an antibody mimetic.

7. The antibody according to claim 6, wherein the antibody mimetic is selected from affibodies, adnectins, anticalins, DARPins, avimers, nanofitins, affilins, Kunitz domain peptides, Fynomers®, and trispecific binding molecules and probodies.

8. The antibody according to claim 6, wherein the drug is selected from erlotinib (TARCEVA; Genentech/OSI Pharm.), bortezomib (VELCADE; MilleniumPharm.), fulvestrant (FASLODEX; AstraZeneca), sutent (SU11248; Pfizer), letrozole (FEMARA; Novartis), imatinib mesylate (GLEEVEC; Novartis), PTK787/ZK 222584 (Novartis), oxaliplatin (Eloxatin; Sanofi), 5-fluorouracil (5-FU, leucovorin, rapamycin (Sirolimus, RAPAMUNE; Wyeth), lapatinib (TYKERB, GSK572016; GlaxoSmithKline), lonafarnib (SCH 66336), sorafenib (BAY43-9006; Bayer Labs.), gefitinib (IRESSA; AstraZeneca), AG1478, AG1571 (SU 5271; Sugen), alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimine and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially, bullatacin and bullatacinone); camptothecin (inclucing the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrousureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g, calicheamycin, especially calicheamycin gamma1 I and calicheamycin omegaI1(see, e.g., Agnew, Chem Intl ed Engl., 33: 183-186 (1994)) and dynemicin, including dynemicin A; bisphosphonate such as clodronate; esperamicin, neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, antrmycin, azaserine, bleomycins, cactinomycin, carabicin, carninomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubucin, 6-diazo-5-oxo-L-norleucine, ADRLIMYCIN® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubucin, liposomal doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptomigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites such as 5-fluorouracil(5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, and thiguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals such as aminoglutethimide, mitotane, and trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine;

demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ('Ara-C'); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N. J.) ABRAXANETM cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumber, I11.), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; gemcitabine; 6-thioguanine; mercaptopurine; platinum analogs such as cisplatin, carboplatin; vinblastine; platinum; etoposide, ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DFMO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, solvates and acids thereof.

9. The antibody according to claim 6, wherein the toxin is selected from auristatin (preferably monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF), domains II and HI of Pseudomonas exotoxin A, diphtheria toxin, ricin A, pokeweed antiviral protein, human pancreatic RNAse, geldanamycin, maytansinoids, calicheamycin, daunomycin, doxorubicin, methotrexate, vindesine, SG2285, dolastatin, dolastatin analogue's auristatin, cryptophycin, camptothecin, rhizoxin derivatives, CC-1065, duocarmycin, enediyne antibiotics, esperamicin, epothilone, an amatoxin (such alpha-amanitin), deruxtecan, exatecan analogue's, a pyrrolobenzodiazepin (PBD) dimer and toxoids.

10. A nucleic acid molecule or a set of two nucleic acid molecules, wherein
the nucleic acid molecule encoding the antibody according to any one of claims 1 to 9, and
the set of two nucleic acid molecules, wherein the first nucleic acid molecule encodes the V_H region of the antibody according to any one of claims 1 to 9 and the second nucleic acid molecule encodes the V_L region of the antibody according to any one of claims 1 to 9.

11. A vector comprising the nucleic acid molecule of claim 10 in an expressible form or a vector of a set of two vectors comprising the set of two nucleic acid molecules of claim 10 in an expressible form.

12. A host cell, comprising the nucleic acid molecule or set of two nucleic acid molecules of claim 10 or the vector of the set of two vectors of claim 11, wherein the host cell is preferably an anti-tumor leucocyte and wherein the anti-tumor leucocyte is preferably a chimeric antigen receptor T-cell (CAR T-cell), T-cell-receptor-engineered T-cells (TCR T-cell), chimeric antigen receptor NK-cells

(CAR NK-cell), NK cell receptor-engineered NK cell (NCR NK-cell), TCR/CAR hybrid T-cell, NCR/CAR hybrid NK-cell, tumor-infiltrating lymphocytes (TIL), or CAR macrophage.

13. A method for producing an antibody of any one of claims 1 to 12, comprising
(a) culturing the host of claim 12 under conditions that allow synthesis of said antibody; and
(b) recovering said antibody from said culture.

14. A diagnostic composition or a pharmaceutical composition comprising the antibody of any one of claims 1 to 9, the nucleic acid molecule or set of two nucleic acid molecules of claim 10, the vector or set of two vectors of claim 11 or the host cell of claim 12.

15. Use of the antibody of any one of claims 1 to 9, the nucleic acid molecule or set of two nucleic acid molecules of claim 10, the vector or set of two vectors of claim 11 or the host cell of claim 12 in the manufacture of a medicament for treating, inhibiting or diagnosing *in vivo* a tumor, wherein the tumor is preferably a T-cell neoplasia, lymphoma or leukemia, and is most preferably a T-cell lymphoma or acute lymphocytic leukemia.