

In terms of cancer treatment generally, despite the recent major advances, some difficult to treat solid tumors do not respond to available therapies; either drugs that are the current standard of care, or those newer and initially promising drugs that are currently in clinical testing. Even if patients do respond initially, they often do not experience a long lasting response and seldom result in a full remission or cure. For example, in the case of non-small cell lung cancer, one such unmet need, some 40-50% of all NSCLC do not respond to first line therapy, while another 50% who do respond, do not experience a long lasting response with current 1st line therapies (e.g., including anti-PD1 immunotherapy). Moreover, less than 30-40% of patients remain progression-free after 12 months. Options for further therapy for patients in 2nd/3rd line who have previously received anti-PD-L1 treatment are limited and not fully established. Since chemotherapy options such as docetaxel or platinum based regimen (if not used in 1st line) are of limited benefit.

In view of the available pre-clinical and clinical data, and of the poor outlook for such cancer patients, there is a clear need to identify more efficacious therapies, particularly those therapies with improved tolerability for the patient and targeted specificity for tumor types resistant to presently available therapies. As such, there is a need for new approaches including immunologically active agents with different modes of actions.

Summary of the invention

The present ~~invention~~disclosure is based on the concept that tumor restricted activation of tumor-specific TILs represents a promising modality to the treatment of cancer. ~~Embodiments~~Examples of the ~~invention~~disclosure are bispecific, bivalent molecules which combine binding sites that binds specifically to Fibroblast activation protein (FAP) with low affinity binding sites that binds specifically to CD137 (4-1BB, TNFRSF9) within a single binding molecule. The bispecific molecules of the ~~invention~~disclosure activate, engage with CD137 on T cells only in the context of the cancer stroma of the tumor microenvironment where FAP is expressed.

As discussed in more detail below, one advantage of the molecule of the ~~invention~~disclosure is the improvement of activation of tumor reactive T cells and expansion of existing tumor response to

the tumor microenvironment leading to tumor regression in patients while improving on safety relative to conventional CD137 agonists. By making CD137 engagement conditional on the proximal expression of FAP because of its low affinity, the CD137 activity and recruitment of T cells only occurs in the FAP+ tumor environment of many cancer types. This low affinity engagement is an improvement over other CD137 monovalent approaches because the bivalent molecules of the ~~invention~~disclosure only significantly bind to and activate those tumor residing T-cells in the presence of FAP, causing them to proliferate and secrete IFN γ , thus yielding a better localized tumor-directed immune response. Ultimately, the targeted activity of the CD137/FAP antibody will lead to tumor regression in patients with a well tolerated and improved safety profile relative to conventional CD137 agonists.

Hence, ~~a first aspect of~~ the ~~invention~~disclosure provides an immunoglobulin-like binding molecule having at least one antigen binding site that binds specifically to Fibroblast activation protein (FAP) and at least one antigen binding site that binds specifically to CD137 (4-1BB, TNFRSF9).

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the molecule is bispecific and tetravalent; bivalent for CD137 and bivalent for FAP.

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the antigen binding site that binds specifically to CD137 (4-1BB, TNFRSF9) is part of an immunoglobulin (Ig) molecule and the antigen binding site that binds specifically to Fibroblast activation protein (FAP) comprises one or more scFv(s) fused to N-terminus of the Fc domain, preferably via a peptide linker.

Thus, in one aspect, the present disclosure provides a bispecific and tetravalent binding molecule having two antigen binding sites that bind specifically to CD137 (4-1BB Ligand Receptor, 4-1BB) and two antigen binding sites that binds specifically to Fibroblast Activation Protein (FAP) wherein the antigen binding site that binds specifically to CD137 (4-1BB Ligand Receptor) is part of an immunoglobulin molecule and the antigen binding sites that bind specifically to Fibroblast Activation Protein (FAP) comprise two scFv(s).

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the one or more scFv(s) have a VL-VH orientation from N-to C-terminus.

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the one or more scFv(s) are fused to the C- terminus of the heavy chain of the Ig molecule.

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the Ig molecule is IgG1KO.

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the one or more scFv(s) is fused to the Ig molecule by a peptide linker, preferably a peptide linker having a length of. about 4 to 20 amino acids

In a preferred ~~embodiment~~example of the binding molecule of the ~~invention~~disclosure, the antigen binding molecule that binds specifically to CD137 (4-1BB) is selected from a group comprising:

i) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:290 (CDR1), SEQ ID NO.:8 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:12 (CDR1), SEQ ID NO.:13 (CDR2) and SEQ ID NO.:14 (CDR3); or ii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:18 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:22 (CDR1), SEQ ID NO.:23 (CDR2) and SEQ ID NO.:14 (CDR3); or

iii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:28 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:32 (CDR1), SEQ ID NO.:33 (CDR2) and SEQ ID NO.:14 (CDR3); or iv) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:38 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:42 (CDR1), SEQ ID NO.:43 (CDR2) and SEQ ID NO.:14 (CDR3); or v) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:48 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:52 (CDR1), SEQ ID NO.:53 (CDR2) and SEQ ID NO.:14 (CDR3); or

vi) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:58 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the

xii) heavy chain CDRs comprising of SEQ ID NO.:308 (CDR1), SEQ ID NO.:338 (CDR2) wherein X1 is selected from the group consisting of Y or I, and SEQ ID NO.:69 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:669 (CDR1) wherein X1 is selected from the group consisting of N or Q, SEQ ID NO.:339 (CDR2) wherein X1 is selected from the group consisting of L or G, and SEQ ID NO.:74 (CDR3); or

xiii) a CD137 antigen binding molecule which binds an epitope on CD137 in the extracellular domain CRD3 between amino acids 87-118 (SEQ ID NO.:352) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(xii); or

xvi) a CD137 antigen binding molecule which binds to an epitope on CD137 in the extracellular domain CRD2/CRD3 between amino acids 46-117 (SEQ ID NO.:356) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(xvi).

In a preferred ~~embodiment~~example of the immunoglobulin-like binding molecule of the ~~invention~~disclosure, the antigen binding site that binds specifically to CD137 (4-1BB) is part of an immunoglobulin molecule comprising a variable heavy chain region and variable light chain region, wherein the VH and VL regions are selected from a group comprising:

i) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:10 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:15; or

ii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:20 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:25; or

iii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:30 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:35; or

from the group consisting of SEQ ID NO.:75, SEQ ID NO.:85, SEQ ID NO.:95, and SEQ ID NO.:105; or

(xv) a CD137 antigen binding molecule which binds an epitope on CD137 in the extracellular domain CRD3 between amino acids 87-118 (SEQ ID NO.:352) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(xiv); or

(xvi) a CD137 antigen binding molecule which binds to an epitope on CD137 in the extracellular domain CRD2/CRD3 between amino acids 46-117 (SEQ ID NO.:356) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(xiv).

In a preferred embodiment example of the binding molecule of the invention disclosure, the antigen binding site that binds specifically to Fibroblast Activation Protein (FAP) is selected from a group of scFvs comprising:

i) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:108 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:111 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or

ii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:117 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:120 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or

iii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:126 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:129 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or

iv) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:328 (CDR1), SEQ ID NO.:135 (CDR2) and SEQ ID NO.:136 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:138 (CDR1), SEQ ID NO.:139 (CDR2) and SEQ ID NO.:140 (CDR3); or

v) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:333 (CDR1), SEQ ID NO.:144 (CDR2) and SEQ ID NO.:145 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:138 (CDR1), SEQ ID NO.:139 (CDR2) and SEQ ID NO.:140 (CDR3); or

vi) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:341 (CDR2) wherein X1 is selected from D or E, and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:691 (CDR1) wherein X1 is selected from the group consisting of N, R, or S, and X2 is selected from is selected from N or S, and SEQ ID NO.:112 (CDR2), and SEQ ID NO.:113 (CDR3); or

vii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:694 (CDR1) wherein X1 is selected from the group consisting of S or N, SEQ ID NO.:342 (CDR2) wherein X1 is selected from the group consisting of D or E, and SEQ ID NO.:343 (CDR3) wherein X1 is selected from N or E, and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:138 (CDR1), and SEQ ID NO.:139 (CDR2) and SEQ ID NO.:140 (CDR3); or

In a preferred embodiment example of the binding molecule of the invention disclosure, the antigen binding site that binds specifically to Fibroblast activation protein (FAP) is selected from a group of scFvs comprising:

i) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:106 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:110; or

viii) a variable heavy chain region VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:106, SEQ ID NO.:115, and SEQ ID NO.:124, and a light chain variable region VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:110, SEQ ID NO.:119, and SEQ ID NO.:128; or

viv) a variable heavy chain region VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:133 and SEQ ID NO.:142, and a light chain variable region VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:137 and SEQ ID NO.:146.

A preferred ~~embodiment~~example of the immunoglobulin-like binding molecule of the ~~invention~~disclosure, comprises a first antigen binding site that binds specifically to CD137 (4-1BB) and a second antigen binding site that binds specifically to Fibroblast Activation Protein (FAP) selected from a group comprising:

i) (a) a CD137 binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:290 (CDR1), SEQ ID NO.:8 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:12 (CDR1), SEQ ID NO.:13 (CDR2) and SEQ ID NO.:14 (CDR3); and

(b) a FAP binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:108 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:111 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or

ii) (a) a CD137 binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:290 (CDR1), SEQ ID NO.:8 (CDR2) and SEQ ID NO.:9

comprising the amino acid sequences of SEQ ID NO.: 669 (CDR1) wherein X1 is selected from the group consisting of N or Q, SEQ ID NO.:339 (CDR2) wherein X1 is selected from the group consisting of L or G, and SEQ ID NO.:74 (CDR3); and

(b) a FAP binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:694 (CDR1) wherein X1 is selected from the group consisting of S or N, SEQ ID NO.:342 (CDR2) wherein X1 is selected from the group consisting of D or E, and SEQ ID NO.:343 (CDR3) wherein X1 is selected from N or E and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:138 (CDR1), SEQ ID NO.:139 (CDR2), and SEQ ID NO.:140 (CDR3).

~~A further aspect of the invention~~The disclosure also provides an immunoglobulin-like binding molecule comprising

(i) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:151, and a light chain comprising the amino acid sequence of SEQ ID NO.:152; or

(ii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:153, and a light chain comprising the amino acid sequence of SEQ ID NO.:154; or

(iii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:155, and a light chain comprising the amino acid sequence of SEQ ID NO.:156; or

(iv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:157, and a light chain comprising the amino acid sequence of SEQ ID NO.:158; or

(v) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:159, and a light chain comprising the amino acid sequence of SEQ ID NO.:160; or

the CDRL1 SEQ ID NO.:691 by an amino acid substitution of not more than two amino acids wherein X1 is selected from the group consisting of N, R, or S, and X2 is selected from is selected from N or S; and

(b) a second polypeptide comprising a light chain which specifically binds to CD137 comprising the amino acid sequence of SEQ ID NO.:154; which differs in amino acid sequence from the CDRL1 SEQ ID NO.:669 by an amino acid substitution of not more than one amino acid wherein X1 is selected from the group consisting of N or Q, and /or the CDRL2 SEQ ID NO.:339 by an amino acid substitution of not more than one amino acids wherein X1 is selected from the group consisting of L or G.

In a further aspect, the present disclosure provides an immunoglobulin-like binding molecule comprising

(i) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:159, and a light chain comprising the amino acid sequence of SEQ ID NO.:160; or

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(ii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:164, and a light chain comprising the amino acid sequence of SEQ ID NO.:165; or

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(iii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:169, and a light chain comprising the amino acid sequence of SEQ ID NO.:170; or

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(iv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:174, and a light chain comprising the amino acid sequence of SEQ ID NO.:175; or

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(v) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:179, and a light chain comprising the amino acid sequence of SEQ ID NO.:180; or

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(vi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:184, and a light chain comprising the amino acid sequence of SEQ ID NO.:185; or

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(vii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:189, and a light chain comprising the amino acid sequence of SEQ ID NO.:190; or

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(viii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:194, and a light chain comprising the amino acid sequence of SEQ ID NO.:195; or

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(ix) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:199, and a light chain comprising the amino acid sequence of SEQ ID NO.:200; or

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(x) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:204, and a light chain comprising the amino acid sequence of SEQ ID NO.:205; or

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(xi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:209, and a light chain comprising the amino acid sequence of SEQ ID NO.:210; or

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(xii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:214, and a light chain comprising the amino acid sequence of SEQ ID NO.:215; or

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(xiii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:219, and a light chain comprising the amino acid sequence of SEQ ID NO.:220; or

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(xiv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:224; and a light chain comprising the amino acid sequence of SEQ ID NO.:225; or

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(xv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:229; and a light chain comprising the amino acid sequence of SEQ ID NO.:230; or

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(xvi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:234; and a light chain comprising the amino acid sequence of SEQ ID NO.:235; or

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(xvii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:239; and a light chain comprising the amino acid sequence of SEQ ID NO.:240; or

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(xviii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:244; and a light chain comprising the amino acid sequence of SEQ ID NO.:245; or

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(xix) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:249; and a light chain comprising the amino acid sequence of SEQ ID NO.:250; or

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(xx) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:254; and a light chain comprising the amino acid sequence of SEQ ID NO.:255; or

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(xxi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:259; and a light chain comprising the amino acid sequence of SEQ ID NO.:260.

~~Thus, in a further aspect, the invention~~The disclosure also provides a bispecific antigen binding molecule, wherein

- (i) each of the polypeptides capable of specific binding to CD137 comprise
 - (a) a heavy chain variable region VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:10, SEQ ID NO.:20, SEQ ID NO.:30, SEQ ID NO.:40, SEQ ID NO.:50, and SEQ ID NO.:60 and a light chain variable region VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:15,, SEQ ID NO.:25, SEQ ID NO.:35, SEQ ID NO.:45, SEQ ID NO.:55, SEQ ID NO.:65; or
 - (b) a variable heavy chain region VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:70, SEQ ID NO.:80, SEQ ID NO.:90, and SEQ ID NO.:100, and a light chain variable region VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%,

99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:75, SEQ ID NO.:85, SEQ ID NO.:95, and SEQ ID NO.:105; and

- (ii) each of the polypeptides capable of specific binding to FAP comprise
 - (a) a variable heavy chain region VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid

sequence select from the group consisting of SEQ ID NO.:106, SEQ ID NO.:115, and SEQ ID NO.:124, and a light chain variable region VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:110, SEQ ID NO.:119, and SEQ ID NO.:128; or

- (b) a variable heavy chain region VH comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:133 and SEQ ID NO.:142, and a light chain variable region VL comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence select from the group consisting of SEQ ID NO.:137 and SEQ ID NO.:146.

In a further aspect, the present disclosure provides a CD137/FAP binding molecule, wherein the CD137 binding portion comprises a heavy chain variable region and a light chain variable region, wherein:

(i) the heavy chain variable region comprises an amino acid sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100; or

(ii) the light chain variable region comprises an amino acid sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 25, 35, 45, 55, 65, 75, 85, 95 and 105; or

(iii) the resulting molecule binds to human CD137 with a K_D of $1 \times 10^{-7}M$ or less; or

(iv) the resulting molecule does not substantially mediate CD137 clustering and T cell activation in the absence of FAP binding; or

(v) the resulting molecule binds an epitope on CD137 in the extracellular domain CRD3 between amino acids 87-118 (SEQ ID NO.:352) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(iv); or

(vi) the resulting molecule binds to an epitope on CD137 in the extracellular domain CRD2/CRD3 between amino acids 46-117 (SEQ ID NO.:356) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(iv).

~~A further aspect of the invention~~The disclosure also provides a nucleic acid molecule or nucleic acid molecules encoding an immunoglobulin-like binding molecule of the ~~invention~~disclosure or an expression vector or expression vectors containing such a nucleic acid molecule. In a further aspect, the present disclosure provides a nucleic acid molecule or multiple nucleic acid molecules encoding a binding molecule as described herein or an expression vector or expression vectors containing such a nucleic acid molecule or nucleic acid molecules. The term “vector” or “expression vector” is synonymous with “expression construct” and refers to a DNA molecule that is used to introduce and direct the expression of a specific gene to which it is operably associated in a target cell. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. The expression vector of the present ~~invention~~disclosure comprises an expression cassette. The term “expression cassette” refers to a polynucleotide generated recombinantly or synthetically, with a series of specified nucleic acid elements that permit transcription of a particular nucleic acid in a target cell. The recombinant expression cassette can be incorporated into a plasmid, chromosome, mitochondrial DNA, plastid DNA, virus, or nucleic acid fragment. Typically, the recombinant

expression cassette portion of an expression vector includes, among other sequences, a nucleic acid sequence to be transcribed and a promoter. In certain ~~embodiment~~examples, the expression cassette of the ~~invention~~disclosure comprises polynucleotide sequences that encode bispecific antigen binding molecules of the ~~invention~~disclosure or fragments thereof; typically multiple expression vectors encoding different portions (e.g., heavy chain and light chains are encoded in different expression vectors) of the immunoglobulin-like binding molecule of the ~~invention~~disclosure are transfected into the same host cell at

the same time. Expression vectors allow transcription of large amounts of stable mRNA. Once the expression vector is inside the target cell, the ribonucleic acid molecule or protein that is encoded by the gene is produced by the cellular transcription and/or translation machinery. In one ~~embodiment~~example, the expression vector or vectors of the ~~invention~~disclosure comprises an expression cassette or cassettes that comprises polynucleotide sequences that encode bispecific antigen binding molecules of the ~~invention~~disclosure or fragments thereof.

~~A further aspect of the invention~~The disclosure also provides a host cell containing a nucleic acid molecule of the ~~invention~~disclosure in functional association with an expression control sequence. In a further aspect, the present disclosure provides a host cell containing a nucleic acid molecule as described herein. The terms "host cell", "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein. A host cell is any type of cellular system that can be used to generate the bispecific antigen binding molecules of the present ~~invention~~disclosure. Host cells include cultured cells, e.g. mammalian cultured cells, such as CHO cells, or hybridoma cells, yeast cells, insect cells, and plant cells, to name only a few, but also cells comprised within a transgenic animal or animal tissue.

~~A further aspect of the invention~~In a further aspect, the present disclosure provides a method of production of a binding molecule of the ~~invention~~disclosure, as described herein before comprising ~~the steps of:~~

- (a) cultivating the host cell of the ~~invention~~disclosure under conditions allowing expression of the molecule; and,
- (b) recovering the molecule.

~~A further aspect of the invention~~The disclosure also provides an immunoglobulin-like binding molecule of the ~~invention~~disclosure, for use in medicine. In a further aspect, the present disclosure provides a binding molecule as described herein, for use in medicine.

The term "cancer" as used herein refers to proliferative diseases, such as lymphomas, lymphocytic leukemias, lung cancer, non-small cell lung (NSCL) cancer, bronchioloalviolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwannomas, ependymomas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenoma and Ewings sarcoma, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. ~~A further aspect of the invention~~The disclosure also provides an immunoglobulin-like binding molecule of the ~~invention~~disclosure, for use in the therapy of cancer, preferably colorectal cancer (CRC) (e.g, colorectal adenocarcinoma), gastric cancer (GC) (e.g., gastric adenocarcinoma), pancreatic cancer (PAC) (e.g., pancreatic adenocarcinoma), and lung cancer (LC) (e.g., lung squamous cell carcinoma, lung adenocarcinoma). In a further aspect, the present disclosure provides a binding molecule as described herein, for use in the therapy of cancer, preferably colorectal cancer (CRC) (e.g, colorectal adenocarcinoma), gastric cancer (GC) (e.g., gastric adenocarcinoma), pancreatic cancer (PAC) (e.g., pancreatic adenocarcinoma), and lung cancer (LC) (e.g., lung squamous cell carcinoma, lung adenocarcinoma). ~~A further aspect of the invention~~The disclosure also provides a pharmaceutical composition, comprising an immunoglobulin-like binding molecule according to any one of the ~~embodiments~~examples of the ~~invention~~disclosure together with a pharmaceutically acceptable

carrier and optionally one or more further active ingredients, e.g. a chemotherapeutic agent, radiation and/or other agents for use in cancer immunotherapy. In a further aspect, the present disclosure provides a pharmaceutical composition, comprising a binding molecule as described herein together with a pharmaceutically acceptable carrier and optionally one or more further active ingredients.

~~In one aspect, provided~~Provided is a bispecific, immunoglobulin-like binding molecule according to any one of the ~~embodimentsexamples~~ as described or a pharmaceutical composition comprising said immunoglobulin-like binding molecule of the ~~invention~~disclosure, for use in stimulation of a T cell response; supporting survival and/or recruitment of activated T cells; preventing suppression and/or anergy of immune cells; treatment of infections, treatment of cancer; delaying the progression of cancer; and/or prolonging the survival of a patient suffering from cancer.

~~A further aspect of the invention~~The disclosure also provides a method of treatment of cancer comprising administering an effective amount of an immunoglobulin-like binding molecule of the ~~invention~~disclosure to a patient in need thereof.

In another aspect, the present disclosure provides use of a binding molecule as described herein in the manufacture of a medicament for the treatment of cancer.

BRIEF DESCRIPTION OF THE FIGURES

FIG 1A-B: **A.** Schematic representation of the Doppelmab immunoglobulin-like binding molecule of the invention. **B.** Schematic of the mode of action of CD137/FAP binding molecules in tumor stroma, where CD137 agonist activity would be restricted to microenvironments expressing FAP+ stromal cells.

FIG 2A-B: **A. Binding of anti-human CD137 antibodies to surface expressed cynomolgus CD137:** Representative clones CD137 #B13, B17, B19, B20, B21, B27, B28, B30, and B31 expressed as mean fluorescent intensity over increasing Ab concentration (nM); **B. Binding of anti-human CD137 antibodies to surface expressed human CD137** Representative clones CD137 #B13, B17, B19, B20, B21, B27, B28, B30, B31 expressed as mean fluorescent intensity over increasing Ab concentration (nM).

FIG 3A-D: Cross-linking-dependent activity of CD137 molecules **A.** EC₅₀ Graph of Anti-CD137 Purified Chimeric IgG Agonistic Activation with (CL+) and without secondary antibody (CL-) crosslinking. Representative clones CD137#A16, A17, A18, A19, A20, A21, A49, A51, A50, A53, A54, and A57. **B.** Bar graphs of Anti-CD137 Purified Chimeric IgG Agonistic Activation with (+) and without (-) secondary antibody. (C) Activity in the Jurkat NFκB assay measured as RLU demonstrating agonist activity only with secondary antibody cross-linking. Positive controls are Urelumab chimeric IgG1-KO, and Utomilumab as IgG1-KO. Representative anti-CD137 clones include #B2, B5, B7, B9, B10, B12, B13, B17, B19, B27, B30, B31, A1, A13, A2, A25, A3, A30, A39, A4, A47, B3, B4, B21, A12, A16, A17, A19, A26, A27, A41, A44, A45, A46, A49, A57, A8, A34, and A35. **C.** Activity in the Jurkat NFκB assay measured as RLU demonstrating agonist activity only without secondary antibody cross-linking.

CLAIMS

1. A bispecific and tetravalent binding molecule having two antigen binding sites that bind specifically to CD137 (4-1BB Ligand Receptor, 4-1BB) and two antigen binding sites that binds specifically to Fibroblast Activation Protein (FAP) wherein the antigen binding site that binds specifically to CD137 (4-1BB Ligand Receptor) is part of an immunoglobulin molecule and the antigen binding sites that bind specifically to Fibroblast Activation Protein (FAP) comprise two scFv(s).
2. The binding molecule of claim 1 wherein the two or more scFv(s) have a VL-VH orientation from N-to C-terminus.
3. The binding molecule of claim 1 wherein each of the two scFv(s) are fused to the C-terminus of the heavy chain of the Ig molecule.
4. The binding molecule of claim 1 wherein the Ig molecule is IgG.
5. The binding molecule of claim 1 wherein the two scFv(s) are fused to the Ig molecule by a peptide linker, having a length of between 4 to 20 amino acids.
6. The binding molecule of any of the previous claims wherein the antigen binding site that binds specifically to CD137 (4-1BB) is part of an immunoglobulin molecule selected from a group comprising heavy chain and light chain variable regions comprising:
 - i) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:290 (CDR1), SEQ ID NO.:8 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:12 (CDR1), SEQ ID NO.:13 (CDR2) and SEQ ID NO.:14 (CDR3); or
 - ii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:18 (CDR2) and SEQ ID NO.: 9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:22 (CDR1), SEQ ID NO.:23 (CDR2) and SEQ ID NO.:14 (CDR3); or
 - iii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:28 (CDR2) and SEQ ID

NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:32 (CDR1), SEQ ID NO.33 (CDR2) and SEQ ID NO.:14 (CDR3); or

iv) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:38 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:42 (CDR1), SEQ ID NO.43 (CDR2) and SEQ ID NO.:14 (CDR3); or

v) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:48 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:52 (CDR1), SEQ ID NO.53 (CDR2) and SEQ ID NO.:14 (CDR3); or

vi) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:295 (CDR1), SEQ ID NO.:58 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:62 (CDR1), SEQ ID NO.:63 (CDR2) and SEQ ID NO.:14 (CDR3); or

vii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:308 (CDR1), SEQ ID NO.:68 (CDR2) and SEQ ID NO.:69 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:72 (CDR1), SEQ ID NO.:73 (CDR2) and SEQ ID NO.:74 (CDR3); or

viii) heavy chain CDRs comprising of SEQ ID NO.:308 (CDR1), SEQ ID NO.:78 (CDR2) and SEQ ID NO.:69 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:72 (CDR1), SEQ ID NO.:73 (CDR2) and SEQ ID NO.:74 (CDR3); or

ix) heavy chain CDRs comprising of SEQ ID NO.:308 (CDR1), SEQ ID NO.:88 (CDR2) and SEQ ID NO.:69 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:92 (CDR1), SEQ ID NO.:93 (CDR2) and SEQ ID NO.:74 (CDR3); or

x) heavy chain CDRs comprising of SEQ ID NO.:308 (CDR1), SEQ ID NO.:98 (CDR2) and SEQ ID NO.:69 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:92 (CDR1), SEQ ID NO.:93 (CDR2) and SEQ ID NO.:74 (CDR3).

7. The binding molecule of any of the previous claims wherein the antigen binding site that binds specifically to CD137 (4-1BB) is part of an immunoglobulin (Ig) molecule selected from a group comprising:

- 5 i) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:10 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:15; or
- ii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:20 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:25; or
- 10 iii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:30 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:35; or
- iv) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:40 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:45; or
- 15 v) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:50 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:55; or
- vi) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:60 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:65; or
- 20 vii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:70 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:75; or
- viii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:80 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:85; or
- 25 ix) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:90 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:95; or
- 30 x) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:100 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:105.

8. The binding molecule of any of the previous claims wherein the antigen binding site that binds specifically to Fibroblast Activation Protein (FAP) is selected from a group of scFvs comprising:

- 5 i) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:108 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:111 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or
- 10 ii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:117 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:120 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or
- 15 iii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:319 (CDR1), SEQ ID NO.:126 (CDR2) and SEQ ID NO.:109 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:129 (CDR1), SEQ ID NO.:112 (CDR2) and SEQ ID NO.:113 (CDR3); or
- 20 iv) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:328 (CDR1), SEQ ID NO.:135 (CDR2) and SEQ ID NO.:136 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:138 (CDR1), SEQ ID NO.:139 (CDR2) and SEQ ID NO.:140 (CDR3); or
- 25 v) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:333 (CDR1), SEQ ID NO.:144 (CDR2) and SEQ ID NO.:145 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:138 (CDR1), SEQ ID NO.:139 (CDR2) and SEQ ID NO.:140 (CDR3).

- 30 9. The binding molecule of any of the previous claims wherein the antigen binding site binding site that binds specifically to Fibroblast Activation Protein (FAP) is selected from a group comprising:

- i) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:106 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:110; or
- 5 ii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:115 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:119; or
- 10 iii) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:124 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:128; or
- iv) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:133 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:137; or
- 15 v) a variable heavy chain comprising the amino acid sequence of SEQ ID NO.:142 and a variable light chain comprising the amino acid sequence of SEQ ID NO.:146.
10. An immunoglobulin-like binding molecule comprising
- (i) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:159, and a light chain comprising the amino acid sequence of SEQ ID NO.:160; or
- 20 (ii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:164, and a light chain comprising the amino acid sequence of SEQ ID NO.:165; or
- 25 (iii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:169, and a light chain comprising the amino acid sequence of SEQ ID NO.:170; or
- 30 (iv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:174, and a light chain comprising the amino acid sequence of SEQ ID NO.:175; or

(v) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:179, and a light chain comprising the amino acid sequence of SEQ ID NO.:180; or

5 (vi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:184, and a light chain comprising the amino acid sequence of SEQ ID NO.:185; or

10 (vii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:189, and a light chain comprising the amino acid sequence of SEQ ID NO.:190; or

15 (viii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:194, and a light chain comprising the amino acid sequence of SEQ ID NO.:195; or

(ix) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:199, and a light chain comprising the amino acid sequence of SEQ ID NO.:200; or

20 (x) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:204, and a light chain comprising the amino acid sequence of SEQ ID NO.:205; or

25 (xi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:209, and a light chain comprising the amino acid sequence of SEQ ID NO.:210; or

30 (xii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:214, and a light chain comprising the amino acid sequence of SEQ ID NO.:215; or

(xiii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:219, and a light chain comprising the amino acid sequence of SEQ ID NO.:220; or

5 (xiv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:224; and a light chain comprising the amino acid sequence of SEQ ID NO.:225; or

10 (xv) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:229; and a light chain comprising the amino acid sequence of SEQ ID NO.:230; or

15 (xvi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:234; and a light chain comprising the amino acid sequence of SEQ ID NO.:235; or

(xvii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:239; and a light chain comprising the amino acid sequence of SEQ ID NO.:240; or

20 (xviii) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:244; and a light chain comprising the amino acid sequence of SEQ ID NO.:245; or

25 (xix) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:249; and a light chain comprising the amino acid sequence of SEQ ID NO.:250; or

30 (xx) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:254; and a light chain comprising the amino acid sequence of SEQ ID NO.:255; or

(xxi) an immunoglobulin heavy chain fused to a scFv at its C-terminus comprising the amino acid sequence of SEQ ID NO.:259; and a light chain comprising the amino acid sequence of SEQ ID NO.:260.

11. A CD137/FAP binding molecule, wherein the CD137 binding portion comprises a heavy chain variable region and a light chain variable region, wherein:

(i) the heavy chain variable region comprises an amino acid sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100; or

(ii) the light chain variable region comprises an amino acid sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 25, 35, 45, 55, 65, 75, 85, 95 and 105; or

(iii) the resulting molecule binds to human CD137 with a K_D of $1 \times 10^{-7}M$ or less; or

(iv) the resulting molecule does not substantially mediate CD137 clustering and T cell activation in the absence of FAP binding; or

(v) the resulting molecule binds an epitope on CD137 in the extracellular domain CRD3 between amino acids 87-118 (SEQ ID NO.:352) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(iv); or

(vi) the resulting molecule binds to an epitope on CD137 in the extracellular domain CRD2/CRD3 between amino acids 46-117 (SEQ ID NO.:356) and blocks binding and/or competes for binding with any of the above antigen binding molecules (i)-(iv).

12. The CD137/FAP binding molecule of claim 11, wherein the FAP binding portion comprises a heavy chain variable region and a light chain variable region, wherein:

(i) the heavy chain variable region comprises an amino acid sequence that is at least at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, at least 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 106, 115, 124, 133, and 142; and

(ii) the light chain variable region comprises an amino acid sequence that is at least 90%,
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least
97%, at least 98%, at least 99% homologous to an amino acid sequence selected from the
group consisting of SEQ ID NOs: 110, 119, 128, 137, and 146.

13. A nucleic acid molecule or multiple nucleic acid molecules encoding a binding
molecule of any of the previous claims or an expression vector or expression vectors
containing such a nucleic acid molecule or nucleic acid molecules.

14. A host cell containing a nucleic acid molecule of claim 13.

15. A method of production of a binding molecule of any one of the previous claims,
comprising:

(i) cultivating the host cell of claim 14 under conditions allowing expression of the
molecule; and,

(ii) recovering the molecule.

16. A binding molecule of any of the previous claims, for use in medicine.

17. A binding molecule of any of the previous claims, for use in the therapy of cancer,
preferably colorectal cancer (CRC) (e.g, colorectal adenocarcinoma), gastric cancer (GC)
(e.g., gastric adenocarcinoma), pancreatic cancer (PAC) (e.g., pancreatic adenocarcinoma),
and lung cancer (LC) (e.g., lung squamous cell carcinoma, lung adenocarcinoma).

18. A pharmaceutical composition, comprising a binding molecule of any one of the
previous claims together with a pharmaceutically acceptable carrier and optionally one or
more further active ingredients.

19. ~~A method of~~Use of a binding molecule of any one of claims 1 to 12 in the manufacture of a medicament for the treatment of cancer ~~comprising administering an effective amount of a binding molecule of any one of the previous claims to a patient in need thereof.~~

5 20. The ~~method use~~ of claim 19, wherein ~~said method comprises that~~ the polypeptide capable of specifically binding to CD137 and FAP is to be administered in combination with a PD-1 antibody to a patient in need thereof.