antigen binding moiety is selected from a Fab molecule and a scFv molecule. In a particular embodiment said antigen binding moiety is a Fab molecule. In another particular embodiment said antigen binding moiety is an immunoglobulin molecule. In a more specific embodiment said antigen binding moiety is an IgG class, particularly an $IgG_1$ subclass, immunoglobulin molecule. In certain embodiments said antigen binding moiety is directed to an antigen presented on a tumor cell or in a tumor cell environment, particularly an antigen selected from the group of Fibroblast Activation Protein (FAP), the A1 domain of Tenascin-C (TNC A1), the A2 domain of Tenascin-C (TNC A2), the Extra Domain B of Fibronectin (EDB), Carcinoembryonic Antigen (CEA) and the Melanoma-associated Chondroitin Sulfate Proteoglycan (MCSP).

In one aspect, the disclosure relates to an immunoconjugate comprising a mutant IL-2 polypeptide and an antigen binding moiety, wherein said mutant IL-2 polypeptide is a human IL-2 molecule comprising the amino acid substitutions F42A, Y45A and L72G, numbered relative to the human IL-2 sequence SEQ ID NO: 1; and wherein said antigen binding moiety is an $IgG_1$ subclass immunoglobulin molecule specific for Fibroblast Activation Protein (FAP), comprising (i) the heavy chain variable region sequence of SEQ ID NO: 41 and the light chain variable region sequence of SEQ ID NO: 39; (ii) the heavy chain variable region sequence of SEQ ID NO: 51 and the light chain variable region sequence of SEQ ID NO: 49; (iii) the heavy chain variable region sequence of SEQ ID NO: 111 and the light chain variable region sequence of SEQ ID NO: 109; (iv) the heavy chain variable region sequence of SEQ ID NO: 143 and the light chain variable region sequence of SEQ ID NO: 141; or (iv) the heavy chain variable region sequence of SEQ ID NO: 151 and the light chain variable region sequence of SEQ ID NO: 149.

The disclosure further provides isolated polynucleotides encoding a mutant IL-2 polypeptide or an immunoconjugate as described herein, expression vectors comprising said polynucleotides, and host cells comprising the polynucleotides or the expression vectors.

In another aspect, the disclosure relates to an isolated polynucleotide encoding the immunoconjugate as described herein.

In another aspect, the disclosure relates to a host cell comprising the polynucleotide as described herein.

Also provided is a method of producing a mutant IL-2 polypeptide or an immunoconjugate as described herein, a pharmaceutical composition comprising a mutant IL-2 polypeptide or an immunoconjugate as described herein and a pharmaceutically acceptable carrier, and methods of using a mutant IL-2 polypeptide or an immunoconjugate as described herein.

In another aspect, the disclosure relates to a method of producing an immunoconjugate comprising a mutant IL-2 polypeptide and an antigen binding moiety, comprising culturing the host cell as described herein under conditions suitable for the expression of the immunoconjugate.

In another aspect, the disclosure relates to a pharmaceutical composition comprising the immunoconjugate as described herein and a pharmaceutically acceptable carrier.

In particular, the disclosure encompasses a mutant IL-2 polypeptide or an immunoconjugate as described herein for use in the treatment of a disease in an individual in need thereof. In another aspect, the disclosure relates to the immunoconjugate as described herein for use in the treatment of a disease in an individual in need thereof. In a particular embodiment said disease is cancer. In a particular embodiment the individual is a human.

Also emcompassed by the disclosure is the use of the mutant IL-2 polypeptide or immunoconjugate as described herein for the manufacture of a medicament for treating a disease in an individual in need thereof. In another aspect, the disclosure relates to use of the immunoconjugate as described herein in the manufacture of a medicament for treating cancer.

Further provided is a method of treating disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising a mutant IL-2 polypeptide or an immunoconjugate as described herein. Said disease preferably is cancer.

## Claims

1. An immunoconjugate comprising a mutant IL-2 polypeptide and an antigen binding moiety,
wherein said mutant IL-2 polypeptide is a human IL-2 molecule comprising the amino acid substitutions F42A, Y45A and L72G, numbered relative to the human IL-2 sequence SEQ ID NO: 1; and
wherein said antigen binding moiety is an $IgG_1$ subclass immunoglobulin molecule specific for Fibroblast Activation Protein (FAP), comprising (i) the heavy chain variable region sequence of SEQ ID NO: 41 and the light chain variable region sequence of SEQ ID NO: 39; (ii) the heavy chain variable region sequence of SEQ ID NO: 51 and the light chain variable region sequence of SEQ ID NO: 49; (iii) the heavy chain variable region sequence of SEQ ID NO: 111 and the light chain variable region sequence of SEQ ID NO: 109; (iv) the heavy chain variable region sequence of SEQ ID NO: 143 and the light chain variable region sequence of SEQ ID NO: 141; or (iv) the heavy chain variable region sequence of SEQ ID NO: 151 and the light chain variable region sequence of SEQ ID NO: 149.

2. The immunoconjugate of claim 1, wherein said mutant IL-2 polypeptide further comprises the amino acid substitution T3A and/or the amino acid substitution C125A.

3. The immunoconjugate of claim 1 or 2, wherein said mutant IL-2 polypeptide comprises the sequence of SEQ ID NO: 19.

4. The immunoconjugate of any one of claims 1 to 3, wherein said mutant IL-2 polypeptide is joined at its amino-terminal amino acid to the carboxy-terminal amino acid of one of the immunoglobulin heavy chains.

5. The immunoconjugate of any one of claims 1 to 4, wherein the immunoconjugate comprises not more than one mutant IL-2 polypeptide.

6. The immunoconjugate of any one of claims 1 to 5, wherein the $IgG_1$ subclass immunoglobulin molecule comprises in the Fc domain a modification promoting heterodimerization of two non-identical immunoglobulin heavy chains; wherein the modification is a knob-into-hole modification, comprising a knob modification in one of the immunoglobulin heavy chains and a hole modification in the other one of the

immunoglobulin heavy chains; wherein the knob modification comprises the amino acid substitution T366W in one of the two immunoglobulin heavy chains, and the hole modification comprises the amino acid substitutions T366S, L368A and Y407V in the other one of the two immunoglobulin heavy chains.

7. The immunoconjugate of claim 6, wherein the immunoglobulin heavy chain comprising the knob modification additionally comprises the amino acid substitution S354C, and the immunoglobulin heavy chain comprising the hole modification additionally comprises the amino acid substitution Y349C.

8. The immunoconjugate of any one of claims 1 to 7, wherein the $IgG_1$ molecule comprises in its Fc domain one or more amino acid mutation that reduces the binding affinity of the immunoconjugate to an FcγRIIIa, FcγRI or FcγRIIa receptor; and wherein the $IgG_1$ molecule comprises the amino acid mutations L234A, L235A and P329G.

9. The immunoconjugate of any one of claims 1 to 8, comprising (i) a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 297, a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 299, and a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 233; (ii) a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 301, a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 303, and a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 231; or (iii) a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 315, a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 317, and a polypeptide sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 233.

10. The immunoconjugate of any one of claims 1 to 9, wherein said $IgG_1$ molecule specific for FAP comprises the heavy chain variable region sequence of SEQ ID NO: 111 and the light chain variable region sequence of SEQ ID NO: 109.

11. The immunoconjugate of any one of claims 1 to 10, comprising a polypeptide sequence of SEQ ID NO: 301, a polypeptide sequence of SEQ ID NO: 303, and a polypeptide sequence of SEQ ID NO: 231.

12. The immunoconjugate of any one of claims 1 to 11, wherein the mutant IL-2 polypeptide and the $IgG_1$ molecule are joined by a linker sequence.

13. An isolated polynucleotide encoding the immunoconjugate of any one of claims 1 to 12.

14. A host cell comprising the polynucleotide of claim 13.

15. A method of producing an immunoconjugate comprising a mutant IL-2 polypeptide and an antigen binding moiety, comprising culturing the host cell of claim 14 under conditions suitable for the expression of the immunoconjugate.

16. A pharmaceutical composition comprising the immunoconjugate of any one of claims 1 to 12 and a pharmaceutically acceptable carrier.

17. The immunoconjugate of any one of claims 1 to 12 for use in the treatment of a disease in an individual in need thereof.

18. The immunoconjugate for use of claim 17, wherein said disease is cancer.

19. Use of the immunoconjugate of any one of claims 1 to 12 in the manufacture of a medicament for treating cancer.