Claims

1. A fusion protein comprising:

domain (a) which is a functional fragment of hTRAIL protein sequence, which fragment begins with an amino acid at a position not lower than hTRAIL95, or a sequence having at least 70% identity with said functional fragment; and

domain (b) which is a sequence of an immunostimulating effector peptide, and is selected from the group consisting of

- the pseudodimer of interferon gamma of SEQ. No. 19; and

- the pseudodimer of interferon alpha 2b of SEQ. No. 46;

wherein the sequence of domain (b) is attached at the C-terminus or N-terminus of domain (a); and

wherein said hTRAIL protein sequence is the SEQ. No. 16.

2. The fusion protein according to claim 1 wherein domain (a) comprises the fragment of hTRAIL protein sequence which begins with an amino acid from the range hTRAIL95 to hTRAIL122, inclusive, and ends with the amino acid hTRAIL281.

3. The fusion protein according to claim 1 or 2 wherein domain (a) is selected from the group consisting of sequences corresponding to hTRAIL95-281, hTRAIL114-281, hTRAIL116-281, hTRAIL120-281, hTRAIL121-281 and hTRAIL122-281.

4. The fusion protein according to any of claims 1 to 3, which between domain (a) and domain (b) contains at least one domain (c) comprising a protease cleavage site selected from the group consisting of a sequence recognized by metalloprotease MMP, sequence recognized by urokinase uPA, and combinations thereof.

5. The fusion protein according to claim 4, wherein the sequence recognized by metalloprotease MMP is SEQ. No. 20, and the sequence recognized by urokinase uPA is SEQ. No. 21.

6. The fusion protein according to claims 4 or 5, wherein domain (c) is a combination of the sequence recognized by metalloprotease MMP and the sequence recognized by urokinase uPA located next to each other.

7. The fusion protein according to any one of claims 4 to 6, which between two domains (c) contains a domain (d) of a linker for attachment of PEG

molecule, selected from the group consisting of SEQ. No. 22, SEQ. No. 23, SEQ. No. 24 and SEQ. No. 25.

8. The fusion protein according to any one of claims 4 to 7 which additionally comprises a glycine-serine flexible steric linker between domains (a), (b), (c) and/or (d).

9. The fusion protein according to claim 8, wherein the glycine-serine linker is selected from the group consisting of SEQ. No. 26, SEQ. No. 27, SEQ. No. 28, and SEQ. No. 50.

10. The fusion protein according to claim 1 the amino acid sequence of which is selected from the group consisting of SEQ. No. 12; SEQ. No. 13; SEQ. No. 14; SEQ. No. 15; and SEQ. No. 44.

11. The fusion protein according to any one of the preceding claims, which is a recombinant protein.

12. A polynucleotide sequence, coding the fusion protein defined as in any one of claims 1 to 10.

13. The polynucleotide sequence according to claim 12 optimized for genetic expression in E. coli.

14. The polynucleotide sequence according to claim 13, selected from the group consisting of SEQ. No. 40; SEQ. No. 41; SEQ. No. 42; SEQ. No. 43; and SEQ. No. 48.

15. An expression vector, comprising the polynucleotide sequence according to any one of claims 12 to 14.

16. A host cell, comprising the expression vector as defined in claim 15, wherein the host cell is not within a human body.

17. The host cell according to claim 16, which is a E. coli cell.

18. A pharmaceutical composition, comprising as an active ingredient the fusion protein as defined in any one of claims 1 to 11 in combination with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition as defined in claim 18 in a form for parenteral administration.

20. Use of the fusion protein as defined in any one of claims 1 to 11 for the preparation of a medicament for the treatment of cancer diseases in mammals, including humans.

Claims

1. A fusion protein comprising:

domain (a) which is a functional fragment of hTRAIL protein sequence, which fragment begins with an amino acid at a position not lower than hTRAIL95, or a sequence having at least 70% identity with said functional fragment; and

domain (b) which is a sequence of an immunostimulating effector peptide, and is selected from the group consisting of

- the fragment of interferon alfa 2b of SEQ. No. 17;
- the fragment of interferon gamma of SEQ. No. 18;
- the pseudodimer of interferon gamma of SEQ. No. 19;
- the pseudodimer of interferon alpha 2b of SEQ. No. 46;
- the consensus sequence of interferon alpha of SEQ. No. 47

wherein the sequence of domain (b) is attached at the C-terminus or N-terminus of domain (a) ; and

wherein said hTRAIL protein sequence is the SEQ. No. 16.

2. The fusion protein according to claim 1 wherein domain (a) comprises the fragment of hTRAIL protein sequence which begins with an amino acid from the range hTRAIL95 to hTRAIL122, inclusive, and ends with the amino acid hTRAIL281.

3. The fusion protein according to claim 1 or 2 wherein domain (a) is selected from the group consisting of sequences corresponding to hTRAIL95-281, hTRAIL114-281, hTRAIL116-281, hTRAIL120-281, hTRAIL121-281 and hTRAIL122-281.

4. The fusion protein according to any of claims 1 to 3, which between domain (a) and domain (b) contains at least one domain (c) comprising a protease cleavage site selected from the group consisting of a sequence recognized by metalloprotease MMP, sequence recognized by urokinase uPA, and combinations thereof.

5. The fusion protein according to claim 4, wherein the sequence recognized by metalloprotease MMP is SEQ. No. 20, and the sequence recognized by urokinase uPA is SEQ. No. 21.

6. The fusion protein according to claims 4 or 5, wherein domain (c) is a combination of the sequence recognized by metalloprotease MMP and the sequence recognized by urokinase uPA located next to each other.

7. The fusion protein according to any one of claims 4 to 6, which between two domains (c) contains a domain (d) of a linker for attachment of PEG molecule, selected from the group consisting of SEQ. No. 22, SEQ. No. 23, SEQ. No. 24 and SEQ. No. 25.

8. The fusion protein according to any one of claims 4 to 7 which additionally comprises a glycine-serine flexible steric linker between domains (a), (b), (c) and/or (d).

9. The fusion protein according to claim 9, wherein the glycine-serine linker is selected from the group consisting of SEQ. No. 26, SEQ. No. 27, SEQ. No. 28, and SEQ. No. 50.

10. The fusion protein according to claim 1 the amino acid sequence of which is selected from the group consisting of SEQ. No. 1; SEQ. No. 2; SEQ. No. 3; SEQ. No. 4; SEQ. No. 5; SEQ. No. 6; SEQ. No. 7; SEQ. No. 8; SEQ. No. 9; SEQ. No. 10; SEQ. No. 11; SEQ. No. 12; SEQ. No. 13; SEQ. No. 14; SEQ. No. 15; SEQ. No. 44, and SEQ. No. 45.

11. The fusion protein according to any one of the preceding claims, which is a recombinant protein.

12. A polynucleotide sequence, coding the fusion protein defined as in any one of claims 1 to 10.

13. The polynucleotide sequence according to claim 12, optimized for genetic expression in E. coli.

14. The polynucleotide sequence according to claim 13, selected from the group consisting of SEQ. No. 29; SEQ. No. 30; SEQ. No. 31; SEQ. No. 32; SEQ. No. 33; SEQ. No. 34; SEQ. No. 35; SEQ. No. 36; SEQ. No. 37; SEQ. No. 38; SEQ. No. 39; SEQ. No. 40; SEQ. No. 41; SEQ. No. 42; SEQ. No. 43; SEQ. No. 48, and SEQ. No. 49.

15. An expression vector, comprising the polynucleotide sequence according to any one of claims 12 to 14.

16. A host cell, comprising the expression vector as defined in claim 15; wherein the host cell is not within a human body.

17. The host cell according to claim~~.~~ 16 ~~17~~, which is a E. coli cell.

18. A pharmaceutical composition, comprising as an active ingredient the fusion protein as defined in any one of claims 1 to 11 in combination with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition as defined in claim 18 in a form for parenteral administration.

20. Use of the fusion protein as defined in any one of claims 1 to 11 for the preparation of a medicament for the treatment of cancer diseases in mammals, including humans.