

Claims

1. A recombinant signal sequence comprising (a) the sequence MGRISSGG (SEQ ID NO: 1) or a variant thereof that differs in sequence by 1, 2, or 3 amino acid substitutions, deletions or insertions, and (b) a heterologous signal sequence C-terminal to (a).
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2. A recombinant fusion protein comprising (a) the recombinant signal sequence of claim 1; and (b) a heterologous recombinant protein C-terminal to (a).
3. A recombinant nucleic acid sequence which encodes the recombinant signal sequence
10 of claim 1 or the recombinant fusion protein as defined in claim 2.
4. A recombinant nucleic acid sequence which encodes a signal sequence comprising the sequence MGRISSGG (SEQ ID NO: 1), wherein the nucleic acid sequence has been codon optimised for expression in a host cell.
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5. The recombinant nucleic acid sequence of claim 4, wherein the codon optimised nucleic acid sequence encodes a recombinant signal sequence comprising the sequence MGRISSGG (SEQ ID NO: 1) or a variant thereof that differs in sequence by 1, 2, or 3 amino acid substitutions, deletions or insertions, and (b) a heterologous signal sequence C-
20 terminal to (a).
6. The recombinant nucleic acid sequence of claim 4, wherein the codon optimised nucleic acid sequence encodes a signal sequence comprising the sequence MGRISSGGMFMFKAITTVAALVIATSAMA (SEQ ID NO:34), or a variant thereof that differs
25 in sequence by 1 to 10 amino acid substitutions, deletions or insertions.
7. The recombinant nucleic acid sequence of claim 4, wherein the codon optimised nucleic acid sequence encodes a signal sequence comprising the sequence MGRISSGGMKKTAIAIAVALAGFATVAQA (SEQ ID NO: 55), or a variant thereof that
30 differs in sequence by 1 to 10 amino acid substitutions, deletions or insertions.
8. The recombinant nucleic acid sequence of any one of claims 3 to 7, wherein the nucleic acid sequence has been codon optimised for expression in a host cell and has a Codon Adaptation Index (CAI) of 0.40 or above.

9. A recombinant expression vector comprising the nucleic acid sequence of any one of claims 3 to 8.

5 10. The recombinant expression vector according to claim 9, wherein the signal sequence is operably linked to the recombinant protein.

11. A method for producing a recombinant protein in a host cell comprising:

10 (a) culturing the host cell under conditions that allow expression of the recombinant protein from the recombinant expression vector according to claims 9 or 10 present in the host cell; and

(b) recovering the recombinant protein.

12. A method for controlling the viscosity of a host cell broth that expresses a recombinant protein, comprising:

15 culturing the host cell under conditions that allow expression of the recombinant protein, wherein the host cell comprises a recombinant nucleic acid sequence which encodes (i) a recombinant signal sequence comprising the sequence MGRISGG (SEQ ID NO: 1) or a variant thereof that differs in sequence by 1, 2, or 3 amino acid substitutions, deletions or insertions, and (ii) the recombinant protein.

13. A method for controlling basal expression of a recombinant protein expressed by a host cell broth, comprising: culturing the host cell under pre-induction conditions,

25 wherein the host cell comprises a recombinant nucleic acid sequence which encodes (i) a recombinant signal sequence comprising the sequence MGRISGG (SEQ ID NO: 1) or a variant thereof that differs in sequence by 1, 2, or 3 amino acid substitutions, deletions or insertions, and (ii) the recombinant protein.

14. The method according to claim 12 or 13 wherein the nucleic acid sequence is as defined in any one of claims 3 to 8.

15. The method according to any one of claims 11 to 14, wherein the recombinant protein is recovered from the periplasm or the extracellular media.

5 16. The method according to any one of claims 11 to 15, wherein the signal sequence is operably linked to the recombinant protein.

17. The method according to any one of claims 11 to 16, wherein a pre-induction expression level of the recombinant protein is $\leq 0.5\text{g/L}$; and/or a post-induction expression level of the recombinant protein is $\geq 5\text{g/L}$.

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18. The method according to any one of claims 11 to 17, wherein the signal sequence is cleaved from the recombinant protein.

15 19. The method according to any one of claims 11 to 18, wherein the recombinant protein is an antigen binding protein.

20. The method according to any one of claims 11 to 19, wherein the host cell is a microbial cell with a periplasm.