Claims

1. A recombinant host cell for manufacturing a heterologous protein of interest, wherein the host cell comprises a heterologous polynucleotide sequence encoding the protein of interest and is engineered to overexpress a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 1 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 1.

2. The host cell of claim 1, wherein said helper protein or said functional homologue thereof increases the yield of the model protein SDZ-Fab (SEQ ID NO: 25 and 26) and/or HyHEL-Fab (SEQ ID NO: 29 and 30) compared to the host cell prior to engineering.

3. The host cell of any one of the preceding claims, wherein said polynucleotide is integrated in the genome of said host cell or contained in a vector or plasmid.

4. The host cell of any one of the preceding claims, wherein the overexpression of the polynucleotide is achieved by (i) using a recombinant promoter which drives expression of said polynucleotide or by (ii) modifying a regulatory sequence operably linked to said polynucleotide.

5. The host cell of any one of the preceding claims, wherein the host cell is *Pichia pastoris, Hansenula polymorpha, Trichoderma reesei, Saccharomyces cerevisiae, Kluyveromyces lactis, Yarrowia lipolytica, Pichia methanolica*, *Candida boidinii Komagataella, or Schizosaccharomyces pombe*.

6. The host cell of any one of the preceding claims, wherein 1, 2, 3, 4, 5, 6, 7, 8 or more further helper proteins selected from SEQ ID NO: 4, 2, 3, 5, 6, 7, 8, 9, or 162 or functional homologues thereof are also overexpressed, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 4, 2, 3, 5, 6, 7, 8, 9, or 162.

7. The host cell of any one of the preceding claims, wherein the host cell is engineered to underexpress at least one polynucleotide encoding a KO protein having an amino acid sequence having at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 10, 11 and/or 12, wherein underexpression is achieved by

knocking-out the polynucleotide encoding the KO protein or a functional homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a functional homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a functional homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a functional homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a functional homologue thereof, such as ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences, or post-transcriptional gene silencing.

8. The host cell of any one of the preceding claims, wherein the protein of interest is an enzyme, a therapeutic protein, a food additive or feed additive, or antibody or antibody fragment.

9. The host cell of claim 6, wherein the host cell is engineered to

   (i) overexpress a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 1 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 1 and SEQ ID NO: 2 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 2 and is further engineered to underexpress a polynucleotide encoding a KO protein having an amino acid as shown in SEQ ID NO: 10 or a functional homologue thereof having at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 10, or

   (ii) overexpress a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 4 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 4 and SEQ ID NO: 1 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 1 and is further engineered to underexpress a polynucleotide encoding a KO protein having an amino acid as shown in SEQ ID NO: 10 or a functional homologue

thereof having at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 10,

wherein underexpression is achieved by knocking-out the polynucleotide encoding the KO protein or a functional homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a functional homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a functional homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a functional homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a functional homologue thereof, such as ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences, or post-transcriptional gene silencing.

10. Use of the host cell of any one of the preceding claims for manufacturing a protein of interest.

11. A method of increasing the yield of a protein of interest in a host cell, comprising overexpressing a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 1 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 1.

12. A method of increasing the yield of a protein of interest in a host cell comprising:

- engineering a host cell to overexpress a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 1 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 1,

- engineering said host cell to comprise a heterologous polynucleotide encoding the protein of interest,

- culturing said host cell under suitable conditions to overexpress the helper protein or the functional homologue and the protein of interest, and optionally

- isolating the protein of interest from the cell culture.

13. A method of manufacturing a protein of interest in a host cell comprising:

    - engineering a host cell to overexpress a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 1 or a functional homologue thereof, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 1 , wherein said host cell comprises a heterologous polynucleotide encoding a protein of interest;

    - culturing the host cell under suitable conditions to overexpress the helper protein or the functional homologue and express the protein of interest, and optionally

    - isolating the protein of interest from the cell culture.

14. The method of any one of claims 11-13, wherein the host cell is engineered to underexpress at least one polynucleotide encoding a KO protein having an amino acid having at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 10, 11 and/or 12, wherein underexpression is achieved by knocking-out the polynucleotide encoding the KO protein or a functional homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a functional homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a functional homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a functional homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a functional homologue thereof, such as ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences, or post-transcriptional gene silencing.