Claims

1. A recombinant host cell for manufacturing a heterologous protein of interest, wherein the host cell is engineered to underexpress at least one polynucleotide encoding a KO protein having an amino acid sequence as shown in SEQ ID NO: 10, 11, 12 or a functional homologue thereof compared to the host cell prior to genetic manipulation to achieve underexpression, wherein underexpression is achieved by knocking-out the polynucleotide encoding the KO protein or a homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a 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, wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 10, 11 or 12, and wherein the host cell is engineered to express a heterologous protein of interest.

2. The host cell of claim 1, wherein underexpressing said polynucleotide encoding the KO protein 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 the host cell is a *Pichia pastoris, Hansenula polymorpha, Trichoderma reesei, Saccharomyces cerevisiae, Kluyveromyces lactis, Yarrowia lipolytica, Pichia methanolica*, *Candida boidinii, Komagataella, or Schizosaccharomyces pombe*.

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

5. The host cell of any one of the preceding claims, wherein the host cell comprises at least one polynucleotide encoding a helper protein.

6. The host cell of claim 5, wherein the helper protein has an amino acid sequence as shown in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 162 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, 3, 4, 5, 6, 7, 8, 9, or 162.

7. A host cell obtained by providing a cell which expresses a polynucleotide encoding SEQ ID NO: 10, 11, and/or 12, or a functional homologue thereof and engineering the cell to underexpress said polynucleotide, wherein underexpression is achieved by knocking-out the polynucleotide encoding the KO protein or a homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a 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; and wherein the functional homologue has at least 70% sequence identity to an amino acid sequence as shown in SEQ ID NO: 10, 11 or 12 and further wherein the host cell is engineered to express a heterologous protein of interest.

8. The host cell of any one of the preceding claims, wherein the host cell is engineered to

   (i) underexpress a polynucleotide encoding a protein having an amino acid as shown in SEQ ID NO: 10 or a functional homologue thereof and further 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 and a helper protein having an amino acid sequence as shown in SEQ ID NO: 2 or a functional homologue thereof, or

   (ii) underexpress a polynucleotide encoding a protein having an amino acid as shown in SEQ ID NO: 10 or a functional homologue thereof and further engineered to overexpress a polynucleotide encoding a helper protein having an amino acid sequence as shown in SEQ ID NO: 4 or a functional homologue thereof and SEQ ID NO: 1 or a functional homologue thereof.

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

10. A method of increasing the yield of a heterologous protein of interest in a host cell, comprising underexpressing at least one polynucleotide encoding a KO protein having an amino acid sequence as shown in SEQ ID NO: 10, 11, 12 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: 10, 11 or 12 and wherein

underexpression is achieved by knocking-out the polynucleotide encoding the KO protein or a homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a 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.

11. The method of increasing the yield of a heterologous protein of interest in a host cell of claim 10, further comprising:

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

- culturing said host cell under suitable conditions to express the protein of interest, and optionally

- isolating the protein of interest from the cell culture.

12. A method of producing a heterologous protein of interest in a host cell comprising:

- providing a host cell engineered to underexpress at least one polynucleotide encoding an KO protein having an amino acid sequence as shown in SEQ ID NO: 10, 11, 12 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: 10, 11 or 12, wherein said host cell comprises a heterologous polynucleotide encoding a protein of interest and wherein underexpression is achieved by knocking-out the polynucleotide encoding the KO protein or a homologue thereof from the genome of said host cell, disrupting the polynucleotide encoding the KO protein or a homologue thereof in the host cell, disrupting a promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof, replacing the promoter which is operably linked with said polypeptide encoding the KO protein or a homologue thereof with another promoter which has lower promoter activity, or disrupting expression control sequences of the KO protein or a 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;

- culturing the host cell under suitable conditions to express the heterologous protein of interest, and optionally

- isolating the protein of interest from the cell culture.

13. The method of any one of claims 10-12, wherein the protein of interest is an enzyme, a therapeutic protein, a food additive or feed additive, preferably a detoxifying enzyme.

14. The method of any one of claims 10-13, wherein underexpressing said polynucleotide encoding the KO protein increases the yield of a 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.