CLAIMS

1. A eukaryotic host cell engineered to produce a heterologous protein of interest (POI), which cell is genetically modified to reduce production of at least one endogenous host cell protein (HCP), wherein said at least one HCP includes any one, two or three of a first HCP (HCP1), a second HCP (HCP2), and a third HCP (HCP3), wherein one of said at least one HCP comprises HCP1, comprising a first HCP (HCP1), wherein a) HCP1 comprises the amino acid sequence of SEQ ID NO:1, if the host cell is Komagataella phaffii, or its homologous sequence that is endogenous to a Komagataella host cell.

b) HCP2 comprises the amino acid sequence of SEQ ID NO:3, if the host cell is *Komagataella phaffii*, or its homologous sequence that is endogenous to a Komagataella host cell; and

c) HCP3 comprises the amino acid sequence of SEQ ID NO:5, if the host cell is *Komagataella phaffii*, or its homologous sequence that is endogenous to a Komagataella host cell.

2. The host cell of claim 1, wherein said at least one HCP is HCP1, and additionally HCP2 and/or HCP3.

3. The host cell of claim 1 or 2, which cell is further genetically modified to reduce production of a further HCP which is HCP4, wherein

a) HCP4 comprises the amino acid sequence of SEQ ID NO:7, if the host cell is *Komagataella phaffii*, or its homologous sequence that is endogenous to a Komagataella host cell.

4. The host cell of any of claims 1 to 3, wherein each of the homologous sequences is characterized by at least 50% sequence identity to the respective amino acid sequence.

5. The host cell of any of claims 1 to 4, wherein the host cell is genetically modified by one or more genetic modifications of the host cell genome comprising a disruption, substitution, deletion or knockout of (i) one or more endogenous

polynucleotides, or a part thereof; or (ii) an expression control sequence, preferably wherein said expression control sequence is selected from the group consisting of a promoter, a ribosomal binding site, transcriptional or translational start and stop sequences, an enhancer and activator sequence.

6. The host cell of claim 5, wherein a gene encoding any of said at least one HCP is knocked out by said one or more genetic modifications.

7. The host cell of any one of claims 1 to 6, which is genetically modified to reduce the amount of any of said at least one HCP by at least 50% (mol/mol) compared to the host cell without said modification, preferably by a knockout of a gene encoding any of said at least one HCP.

8. The host cell of any one of claims 1 to 7, which comprises an expression cassette comprising one or more regulatory nucleic acid sequences operably linked to a nucleotide sequence encoding the POI, wherein said one or more operably linked sequences are not naturally associated with the POI encoding sequence.

9. The host cell of any one of claims 1 to 8, wherein the POI is a peptide or protein selected from the group consisting of an antigen-binding protein, a therapeutic protein, an enzyme, a peptide, a protein antibiotic, a toxin fusion protein, a carbohydrate - protein conjugate, a structural protein, a regulatory protein, a vaccine antigen, a growth factor, a hormone, a cytokine, a process enzyme, and a metabolic enzyme.

10. The host cell of any one of claims 1 to 9, which is any one of an animal cell, a vertebrate cell, a mammalian cell, a human cell, a plant cell, a nematodal cell, an invertebrate cell, an insect cell, a mollusc cell, a stem cell derived of any of the foregoing, or a yeast or fungal cell.

11. The host cell of any one of claims 1 to 10, which is

a) a yeast cell of a genus selected from the group consisting of Pichia, Hansenula, Komagataella, Saccharomyces, Kluyveromyces, Candida, Ogataea, Yarrowia, and Geotrichum, such as *Pichia pastoris, Komagataella phaffii,*

Komagataella pastoris, Komagataella pseudopastoris, Saccharomyces cerevisiae, Ogataea minuta, Kluyveromces lactis, Kluyveromes marxianus, Yarrowia lipolytica or *Hansenula polymorpha*; or

b) a cell of filamentous fungi, such as *Aspergillus awamori* or *Trichoderma reesei*.

12. A method for producing a protein of interest (POI) in a eukaryotic host cell, comprising the steps:

a) genetically modifying the host cell to reduce production of at least one endogenous host cell protein (HCP), wherein said at least one HCP includes any one, two or three of a first HCP (HCP1), a second HCP (HCP2), and a third HCP (HCP3), wherein one of said at least one HCP comprises HCP1, wherein HCP1 comprises the amino acid sequence of SEQ ID NO:1, if the host cell is Komagataella phaffii, or its homologous sequence that is endogenous to a Komagataella host cell;

b) HCP2 comprises the amino acid sequence of SEQ ID NO:3, if the host cell is *Komagataella phaffii*, or its homologous sequence that is endogenous to a Komagataella host cell; and

c) HCP3 comprises the amino acid sequence of SEQ ID NO:5, if the host cell is *Komagataella phaffii*, or its homologous sequence that is endogenous to a Komagataella host cell;

i) introducing into the host cell an expression cassette comprising one or more regulatory nucleic acid sequences operably linked to a nucleotide sequence encoding the POI;

ii) culturing said host cell under conditions to produce said POI; and optionally

iii) isolating said POI from the cell culture; and optionally

iv) purifying said POI.

13. A method for producing a protein of interest (POI) by culturing the host cell of any one of claims 1 to 11 under conditions to produce said POI.

14. The method of claim 12 or 13, wherein the amount of any of said at least one HCP is reduced by at least 50% (mol/mol) compared to the host cell without said

modification, preferably by a knockout of a gene encoding any of said at least one HCP.

15. A method of reducing the risk of endogenous host cell protein (HCP) contaminations of a protein of interest (POI) produced in a host cell culture, by culturing the host cell of any one of claims 1 to 11 under conditions to produce said POI and isolating the POI from said cell culture.