CLAIMS

1. A method of manufacturing a heterologous polypeptide product in a cell, the method comprising:

reducing the level of expression of endogenous protein Lamb1, in the cell in an amount sufficient to achieve increased production of the heterologous polypeptide, and,
culturing the cell under conditions suitable for producing the heterologous polypeptide product,

thereby manufacturing the heterologous polypeptide product,

wherein the increased production of the heterologous polypeptide product is an increase in product production rate (qP) of at least 20% compared to a cell of the same type not having a reduced level of endogenous protein.

2. The method of claim 1, further comprising recovering the heterologous polypeptide product.

3. The method of claim 1, wherein the levels of expression of two or more endogenous proteins are decreased.

4. The method of claim 3, wherein the levels of expression of three endogenous proteins are decreased, and wherein the endogenous proteins are: Lamb1, Mfge8 and Sbsn; B2m, C1S and Lamb1; C1S, Den and Lamb1; CIR, Lamb1 and Nid1; or Den, Lamb1 and Nid1.

5. The method of claim 1, wherein reducing the level of expression of the endogenous protein in the cell comprises knocking out a copy of the gene encoding the endogenous protein from the genome of the cell or a regulatory nucleic acid sequence operably coupled to the gene encoding the endogenous protein.

6. The method of claim 5, wherein the knocking out comprises using a CRISPR-Cas9 protein in combination with an RNA specific for the gene encoding the endogenous protein or a regulatory nucleic acid sequence operably coupled to the gene encoding the endogenous protein.

7. The method of claim 1, wherein reducing the level of expression of the endogenous protein in the cell comprises knocking out all copies of the gene encoding the endogenous protein from the genome of the cell or a regulatory nucleic acid sequence operably coupled to the gene encoding the endogenous protein.

8. The method of claim 1, wherein the cell is a Chinese hamster ovary (CHO) cell.

9. The method of claim 1, wherein the increased production of the heterologous polypeptide product is an increase in production titer of at least 20% compared to a cell of the same type not having a reduced level of the endogenous protein.