In certain embodiments, a genetic engineering system for use in the present disclosure is a zinc-finger nuclease (ZFN) system or a transcription activator-like effector nuclease (TALEN) system. In certain non-limiting embodiments, the genetic engineering system includes an RNA selected from the group consisting of a short hairpin RNA (shRNA), a small interference RNA (siRNA) and a micro RNA (miRNA) and the RNA is complementary to an mRNA expressed by the *PKM* gene. In certain embodiments, the mRNA expressed by the *PKM* gene encodes a PKM-1 polypeptide isoform. In certain embodiments, the expression of PKM-1 polypeptide isoform is knocked down, and the lactogenic activity of the cell is reduced. In certain embodiments, the genetic engineering system further comprises a second RNA selected from the group consisting of a shRNA, an siRNA and a microRNA miRNA, wherein the second RNA is complementary to a portion of an mRNA expressed by the *PKM* gene that encodes the PKM-2 polypeptide isoform. In certain embodiments, the expression of PKM-1 and PKM-2 polypeptide isoforms are knocked out or knocked down, and the lactogenic activity of the cell is reduced.

In a further aspect, the present disclosure provides methods for producing a product of interest, *e.g.*, from the cells disclosed herein. For example, a method of producing a product of interest comprises culturing mammalian cells to produce the product of interest, wherein the mammalian cells have reduced or eliminated lactogenic activity. In certain embodiments, the present disclosure provides a method of culturing a population of mammalian cells expressing a product of interest, wherein the mammalian cells have reduced or eliminated lactogenic activity. In certain embodiments, the reduction or elimination of lactogenic activity results from knocking down or knocking out the expression of a pyruvate kinase muscle (PKM) polypeptide isoform in the mammalian cells. In certain embodiments, the PKM polypeptide isoform is the PKM-1 polypeptide isoform. In certain embodiments, expression of the PKM-2 polypeptide isoform is also knocked down or knocked out. In certain embodiments, the method can further comprise isolating the product of interest from the cell culture.

In another aspect, the present disclosure provides a mammalian cell having reduced or eliminated lactogenic activity, wherein the expression of a pyruvate kinase muscle (PKM) polypeptide isoform is knocked down or knocked out, and wherein the PKM polypeptide isoform comprises a PKM-1 polypeptide isoform, wherein the cell is a CHO cell.

In another aspect, the present disclosure provides a composition comprising the mammalian cell as described herein.

In another aspect, the present disclosure provides a method of producing a product of interest, comprising culturing the mammalian cell as described herein, wherein the mammalian cell expresses the product of interest.

In another aspect, the present disclosure provides a method of culturing a population of mammalian cells having reduced or eliminated lactogenic activity, comprising culturing one or more mammalian cells as described herein.

In another aspect, the present disclosure provides a mammalian cell comprising an allele of a *PKM* gene that comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 37-41, wherein the cell is a CHO cell.

In another aspect, the present disclosure provides a method for reducing or eliminating lactogenic activity in a CHO cell, comprising knocking down or knocking out the expression of a pyruvate kinase muscle (PKM) polypeptide isoform.

In another aspect, the present disclosure provides a method of producing a product of interest comprising culturing mammalian cells expressing the product of interest, wherein the mammalian cells express the product of interest and have reduced or eliminated lactogenic activity, wherein the cells are CHO cells.

4. BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1F. Lactate levels of mAb-1 cell line directly correlate with the PKM-1 levels. Percent cell viability (Figure 1A), day 14 titer (Figure 1B), and lactate levels (Figure 1C) in mAb-1 cell line under low and high lactate processes. (Figure 1D) PKM-1 and PKM-2 western blot analysis of mAb-1 cell lysates at different days during production

WHAT IS CLAIMED IS:

1. A mammalian cell having reduced or eliminated lactogenic activity, wherein the expression of a pyruvate kinase muscle (PKM) polypeptide isoform is knocked down or knocked out, and wherein the PKM polypeptide isoform comprises a PKM-1 polypeptide isoform, wherein the cell is a CHO cell.

2. The mammalian cell of claim 1, wherein the expression of a PKM-2 polypeptide isoform is knocked down or knocked out.

~~3. The mammalian cell of claim 1, wherein the cell is a CHO cell.~~

~~4.~~3. The mammalian cell of claim 1, comprising a nucleic acid sequence encoding a product of interest.

~~5.~~4. The mammalian cell of claim 3~~4~~, wherein the product of interest comprises: (i) a protein; (ii) a recombinant protein; (iii) an antibody or an antigen-binding fragment thereof; or (iv) a combination thereof.

~~6.~~5. The mammalian cell of claim 4~~5~~, wherein (i) the antibody is a multispecific antibody or an antigen-binding fragment thereof; or (ii) the antibody consists of a single heavy chain sequence and a single light chain sequence or antigen-binding fragments thereof.

~~7.~~6. The mammalian cell of claim 3~~4~~, wherein the nucleic acid sequence is integrated in the cellular genome of the mammalian cell at a targeted location.

~~8.~~7. The mammalian cell of claim 1, wherein the lactogenic activity of the mammalian cell is less than about 50% or less than about 20% of the lactogenic activity of a reference cell.

~~9.~~8. The mammalian cell of claim 1, wherein the mammalian cell produces less than about 2.0 g/L of lactate during a production phase.

~~10.~~9. A composition comprising the mammalian cell of claim 1.

~~11.~~10. A method of producing a product of interest, comprising culturing the mammalian cell of claim 1, wherein the mammalian cell expresses the product of interest.

~~12.~~11. A method of culturing a population of mammalian cells having reduced or eliminated lactogenic activity, comprising culturing one or more mammalian cells of claim 1.

~~13.~~12. A mammalian cell comprising an allele of a *PKM* gene that comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 37-41, wherein the cell is a CHO cell.

~~14.~~13. The mammalian cell of claim 1~~2~~3, comprising a nucleic acid sequence encoding a product of interest.

~~15.~~14. A composition comprising a mammalian cell of claim 1~~2~~3.

~~16.~~15. A method of producing a product of interest, comprising culturing the mammalian cell of claim 1~~2~~3, wherein the mammalian cell expresses the product of interest.

~~17.~~16. A method of culturing a population of mammalian cells having reduced or eliminated lactogenic activity, comprising culturing one or more mammalian cells of claim 1~~2~~3.

~~18.~~17. A method for reducing or eliminating lactogenic activity in a CHO cell, comprising knocking down or knocking out the expression of a pyruvate kinase muscle (PKM) polypeptide isoform.

~~19.~~18. The method of claim 17~~8~~, wherein a genetic engineering system is administered to the cell for knocking down or knocking out the expression of the pyruvate kinase muscle (PKM) polypeptide isoform.

~~20.~~19. The method of claim 18~~9~~, wherein the genetic engineering system is: (i) a CRISPR/Cas system; (ii) a zinc-finger nuclease (ZFN) system; (iii) a transcription activator-like effector nuclease (TALEN) system; (iv) an RNA selected from the group consisting of a short hairpin RNA (shRNA), a small interference RNA (siRNA), and a microRNA (miRNA), wherein the RNA is complementary to a portion of an mRNA expressed by the *PKM* gene; or (v) a combination thereof.

~~21.~~20. The method of claim 19~~20~~, wherein the genetic engineering system is a CRISPR/Cas9 system comprising: (i) a Cas9 molecule; and (ii) one or more guide RNAs (gRNAs) comprising a targeting sequence that is complementary to a target sequence in a *PKM* gene.

~~22.~~21. The method of claim 20~~1~~, wherein the target sequence is selected from the group consisting of: a portion of the *PKM* gene, a 5' intron region flanking exon 9 of the *PKM* gene, a 3' intron region flanking exon 9 of the *PKM* gene, a 3' intron region flanking exon 10 of the *PKM* gene, a region within exon 1 of the *PKM* gene, a region within exon 2 of the *PKM* gene, a region within exon 12 of the *PKM* gene and combinations thereof.

~~23.~~22. The method of claim 17~~8~~, wherein the cell expresses a product of interest.

~~24.~~23. A method of producing a product of interest comprising culturing mammalian cells expressing the product of interest, wherein the mammalian cells express the product of interest and have reduced or eliminated lactogenic activity, wherein the cells are CHO cells.

~~25.~~24. The method of claim 23~~4~~, wherein the reduction or elimination of lactogenic activity results from the knockout or knockdown of the expression of a pyruvate kinase muscle (PKM) polypeptide isoform in the mammalian cells.

~~26.~~25. The method of claim 24~~5~~, wherein the PKM polypeptide isoform is (i) a PKM-1 polypeptide isoform; ~~(ii) PKM-2 polypeptide isoform;~~ or (ii~~i~~) a PKM-1 polypeptide isoform and a PKM-2 polypeptide isoform.