

product produced by the modified cell during cell culture; can co-purify with the product of interest produced by the modified cell during cell culture; and/or requires removal by purification for product quality and/or safety reasons.

In certain examples, the present disclosure is directed to a modified mammalian cell,
5 wherein the cell is modified to reduce or eliminate the expression of one or more endogenous products relative to the expression of the endogenous products in an unmodified cell, wherein the one or more endogenous products is selected from endogenous virus-like particles such as retrovirus-like particles (RVLPs), e.g., via a reduction or elimination of RVLP group antigen (GAG) expression, and/or one or more of the endogenous protein
10 group consisting of: BCL2 Associated X, Apoptosis Regulator (BAX); BCL2 Antagonist/Killer 1 (BAK); Intercellular Adhesion Molecule 1 (ICAM-1); Protein Kinase R-like ER Kinase (PERK); Sirtuin 1 (SIRT-1); MYC Proto-Oncogene, BHLH Transcription Factor (MYC); Glycoprotein Alpha-Galactosyltransferase 1 (GGTA1); Cytidine Monophosphate-N-Acetylneuraminic Acid Hydroxylase (CMAH); Lipoprotein lipase
15 (LPL); Phospholipase A2 group XV (LPLA2); Palmitoyl-protein thioesterase 1 (PPT1); Branched Chain Keto Acid Dehydrogenase E1 alpha subunit (BCKDHA); Branched Chain Keto Acid Dehydrogenase E1 beta subunit (BCKDHB); and Lipase A (Lysosomal acid lipase/cholesteryl ester hydrolase, Lipase) (LIPA). In one aspect, the present disclosure is directed to a modified mammalian cell, wherein the expression of the expression products
20 selected from the following groupings:

- a) BAX; BAK; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- b) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPL, LPLA2; and PPT1;
- c) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- 25 d) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- e) BAX; BAK; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;

- f) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- g) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- h) BAX; BAK; ICAM-1; LPL; LPLA2; and PPT1;
- 5 i) BAX; BAK; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
- j) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
- k) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and LIPA;
- l) BAX; BAK; ICAM-1; SIRT-1; and MYC;
- m) BAX; BAK; ICAM-1; PERK; SIRT-1; and MYC;
- 10 n) BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- o) BAX; BAK; LPL; LPLA2; GGTA1; and CMAH;
- p) BAX; BAK; PERK; LPL; LPLA2; GGTA1; and CMAH;
- q) BAX; BAK; MYC; LPL; LPLA2; GGTA1; and CMAH;
- 15 r) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
- s) BAX; BAK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- t) BAX; BAK; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- u) BAX; BAK; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- v) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- 20 w) BAX; BAK; ICAM-1; and SIRT-1;
- x) BAX; BAK; and ICAM-1;
- y) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- z) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- 25 aa) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- bb) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- cc) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- 30 dd) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- ee) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;

ff) BAX; BAK; BCKDHA; ICAM-1; LPL; LPLA2; and PPT1;
gg) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
hh) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
ii) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and
5 LIPA;
jj) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; and MYC;
kk) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; and MYC;
ll) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH;
LPL, LPLA2; PPT1; and LIPA;
10 mm) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; and CMAH;
nn) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; and CMAH;
oo) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; and CMAH;
pp) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
qq) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; CMAH; and PPT1;
15 rr) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
ss) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
tt) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;
uu) BAX; BAK; BCKDHA; ICAM-1; and SIRT-1;
20 vv) BAX; BAK; BCKDHA; and ICAM-1;
ww) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPL; LPLA2;
and PPT1;
xx) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and
PPT1;
25 yy) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL;
LPLA2; and PPT1;
zz) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL,
LPLA2; PPT1; and LIPA;
aaa) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPLA2; PPT1;
30 and LIPA;
bbb) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;

ccc) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;

ddd) BAX; BAK; BCKDHB; ICAM-1; LPL; LPLA2; and PPT1;

eee) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;

5 fff) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;

ggg) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2;
PPT1; and LIPA;

hhh) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; and MYC;

iii) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; and MYC;

10 jjj) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH;
LPL, LPLA2; PPT1; and LIPA;

kkk) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;

lll) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;

mmm) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; and CMAH;

15 nnn) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
CMAH;

ooo) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; CMAH; and PPT1;

ppp) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;

20 qqq) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;

rrr) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;

sss) BAX; BAK; BCKDHB; ICAM-1; and SIRT-1;

ttt) BAX; BAK; BCKDHB; and ICAM-1;

25 uuu) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
LPL; LPLA2; and PPT1;

vvv) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPL; LPLA2; and PPT1;

www) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL; LPLA2; and PPT1;

30 xxx) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;

yyy) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;

zzz) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPLA2; PPT1; and LIPA;

5 aaaa) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPLA2; PPT1; and LIPA;

bbbb) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; LPL; LPLA2; and
PPT1;

cccc) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; LPL, LPLA2;
10 and PPT1;

dddd) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
LPLA2; and PPT1;

eeee) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
LPLA2; PPT1; and LIPA;

15 ffff) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; and MYC;

gggg) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1; and
MYC;

hhhh) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1;
MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;

20 iii)BAX; BAK; BCKDHA; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;

jjjj)BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;

kkkk) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
and CMAH;

llll)BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
25 CMAH;

mmmm) BAX; BAK; BCKDHA; BCKDHB; LPL;
LPLA2; GGTA1; CMAH; and PPT1;

nnnn) BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1;
CMAH; and PPT1;

30 oooo) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
CMAH; and PPT1;

pppp) BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2;
GGTA1; CMAH; and PPT1;

qqqq) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; and SIRT-1; or
rrrr) BAX; BAK; BCKDHA; BCKDHB; and ICAM-1
is reduced or eliminated relative to the expression of the endogenous products in an
unmodified cell.

5 In certain examples, the present disclosure is directed to a modified cell of wherein
the expression of RVLPs is reduced or eliminated, e.g., via a reduction or elimination of
RVLP group antigen (GAG) expression.

In certain examples, the present disclosure is directed to a modified cell of wherein
the expression of:

- 10 a) BAX; BAK; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
b) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPL, LPLA2; and PPT1;
c) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and
PPT1;
d) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1;
15 and LIPA;
e) BAX; BAK; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
f) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
g) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and
LIPA;

20

monoclonal antibody. In certain examples, the present disclosure is directed to the above-described modified cells, where the exogenous nucleic acid sequence is integrated in the cellular genome of the mammalian cell at one or more targeted locations.

5 In certain examples, the present disclosure is directed to the above-described modified cells, where the modified cell does not express detectable BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPLA2; PPT1; BCKDHA; BCKDHB; LPL; and/or LIPA. In certain examples, the present disclosure is directed to the above-described modified cells, where the modified cell expresses decreased levels of GAG; BAX; BAK; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; BCKDHA; BCKDHB;
10 LPL; and/or LIPA.

In certain examples, the present disclosure is directed to the above-described modified cells, where the modified cell is a modified mammalian cell. In certain examples, the modified cell is a modified CHO cell. In another example, the modified cell is a modified HEK 293, HEK-293T, BHK, A549 or HeLa cell.

15 In certain examples, the present disclosure is directed to a composition comprising the above-described modified cells. In one aspect, the present disclosure is directed to a composition comprising the modified mammalian cell as disclosed herein.

In certain examples, the present disclosure is directed to a method of producing a recombinant product of interest comprising culturing a modified mammalian cell expressing
20 the recombinant product of interest, wherein the modified cells expressing the recombinant product of interest exhibit reduced or eliminated expression of one or more of the following GAG; BAX; BAK; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH; LPLA2; BCKDHA; BCKDHB; PPT1; LPL; and/or LIPA. In one aspect, the present disclosure is directed to a method of producing a recombinant product of interest comprising: i) culturing the modified
25 mammalian cell as disclosed herein; ii) recovering the recombinant product of interest from the cultivation medium or the modified mammalian cells.

In certain examples, the present disclosure is directed to a method of culturing a population of mammalian cells expressing a recombinant product of interest, wherein the modified cells expressing the recombinant product of interest exhibit reduced or eliminated
30 expression of one or more of the following GAG; BAX; BAK; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; BCKDHA; BCKDHB; LPL; and/or LIPA.

In certain examples, the present disclosure is directed to a method culturing a population of modified mammalian cells expressing a recombinant product of interest or a method of producing a recombinant product of interest comprising culturing a population
35 of mammalian cells expressing a recombinant product of interest, wherein modified cells expressing the recombinant product of interest exhibit reduced or eliminated expression of:
a) BAX; BAK; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;

examples, the modified cell is a modified CHO cell. In certain examples, the modified cell is a modified HEK 293, HEK 293T, BHK, A549, or HeLa cell

In certain examples, the subject matter of the present disclosure is directed to compositions comprising a modified mammalian cell as described herein.

5 In certain examples, the subject matter of the present disclosure is directed to methods of producing a recombinant product of interest comprising: i) culturing a modified mammalian cell comprising an exogenous nucleic acid encoding a recombinant product of interest as described herein; ii) recovering the recombinant product of interest from a cultivation medium or the modified mammalian cells, wherein the modified cells expressing
10 the recombinant product of interest exhibit reduced or eliminated expression of one or more of the following GAG; BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPLA2; PPT1; BCKDHA; BCKDHB; LPL; and/or LIPA.

In certain examples, the present disclosure is directed to methods for producing a modified mammalian cell, comprising: applying a nuclease-assisted and/or nucleic acid targeting at least one endogenous gene selected from the group of genes consisting GAG; BAX; BAK; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; BCKDHA; BCKDHB; LPL; and LIPA, in the mammalian cell to reduce or eliminate the expression of said endogenous gene, and selecting the modified mammalian cell wherein the expression of said endogenous gene has been reduced or eliminated as compared to an unmodified
15 mammalian cell. In one aspect, the present disclosure is directed to a method for producing a modified mammalian cell, comprising: (1) applying a nuclease-assisted and/or nucleic acid targeting at least one endogenous gene selected from the group of genes consisting of

- a) BAX; BAK; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- b) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- 25 c) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- d) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- e) BAX; BAK; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- 30 f) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- g) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- h) BAX; BAK; ICAM-1; LPL; LPLA2; and PPT1;
- i) BAX; BAK; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
- 35 j) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;

- k) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and LIPA;
- l) BAX; BAK; ICAM-1; SIRT-1; and MYC;
- m) BAX; BAK; ICAM-1; PERK; SIRT-1; and MYC;
- n) BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPL, LPLA2;
5 PPT1; and LIPA;
- o) BAX; BAK; LPL; LPLA2; GGTA1; and CMAH;
- p) BAX; BAK; PERK; LPL; LPLA2; GGTA1; and CMAH;
- q) BAX; BAK; MYC; LPL; LPLA2; GGTA1; and CMAH;
- r) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
- s) BAX; BAK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- 10 t) BAX; BAK; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- u) BAX; BAK; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- v) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- w) BAX; BAK; ICAM-1; and SIRT-1;
- x) BAX; BAK; and ICAM-1;
- 15 y) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- z) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and
PPT1;
- aa) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL;
20 LPLA2; and PPT1;
- bb) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL,
LPLA2; PPT1; and LIPA;
- cc) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- dd) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1;
25 and LIPA;
- ee) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2;
PPT1; and LIPA;
- ff) BAX; BAK; BCKDHA; ICAM-1; LPL; LPLA2; and PPT1;
- gg) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
- hh) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
- 30 ii) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and
LIPA;

jj) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; and MYC;
kk) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; and MYC;
ll) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH;
LPL, LPLA2; PPT1; and LIPA;
5 mm) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; and CMAH;
nn) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; and CMAH;
oo) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; and CMAH;
pp) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
qq) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; CMAH; and PPT1;
10 rr) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
ss) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
tt) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;
uu) BAX; BAK; BCKDHA; ICAM-1; and SIRT-1;
15 vv) BAX; BAK; BCKDHA; and ICAM-1;
ww) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPL; LPLA2;
and PPT1;
xx) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and
PPT1;
20 yy) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL;
LPLA2; and PPT1;
zz) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL,
LPLA2; PPT1; and LIPA;
aaa) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPLA2; PPT1;
25 and LIPA;
bbb) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;
ccc) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;
30 ddd) BAX; BAK; BCKDHB; ICAM-1; LPL; LPLA2; and PPT1;
eee) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
fff) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;

ggg) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2;
PPT1; and LIPA;

hhh) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; and MYC;

iii) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; and MYC;

5 jjj) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH;
LPL, LPLA2; PPT1; and LIPA;

kkk) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;

lll) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;

mmm) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; and CMAH;

10 nnn) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
CMAH;

ooo) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; CMAH; and PPT1;

ppp) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;

15 qqg) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
rrr) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;

sss) BAX; BAK; BCKDHB; ICAM-1; and SIRT-1;

ttt) BAX; BAK; BCKDHB; and ICAM-1;

20 uuu) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
LPL; LPLA2; and PPT1;

vvv) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPL; LPLA2; and PPT1;

www) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
25 GGTA1; CMAH; LPL; LPLA2; and PPT1;

xxx) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;

yyy) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;

30 zzz) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPLA2; PPT1; and LIPA;

aaa) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPLA2; PPT1; and LIPA;

bbbb) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; LPL; LPLA2; and
 PPT1;
 cccc) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; LPL, LPLA2;
 and PPT1;
 5 dddd) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
 LPLA2; and PPT1;
 eeee) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
 LPLA2; PPT1; and LIPA;
 ffff) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; and MYC;
 10 gggg) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1; and
 MYC;
 hhhh) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1;
 MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
 iii)BAX; BAK; BCKDHA; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;
 15 jjjj)BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;
 kkkk) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
 and CMAH;
 llll)BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
 CMAH;
 20 mmmm) BAX; BAK; BCKDHA; BCKDHB; LPL;
 LPLA2; GGTA1; CMAH; and PPT1;
 nnnn) BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1;
 CMAH; and PPT1;
 oooo) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
 25 CMAH; and PPT1;
 pppp) BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2;
 GGTA1; CMAH; and PPT1;
 qqqq) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; and SIRT-1; or
 BAX; BAK; BCKDHA; BCKDHB; and ICAM-1
 30 in the mammalian cell to reduce or eliminate the expression of said endogenous
 gene, and (2) selecting the modified mammalian cell wherein the expression of said
 endogenous genes has been reduced or eliminated as compared to an unmodified
 mammalian cell. In certain examples, the nuclease-assisted gene targeting system is selected

from the group consisting of CRISPR/Cas9, CRISPR/Cpf1, zinc-finger nuclease, TALEN or meganuclease.

In certain examples, the modification to the modified mammalian cells described herein is performed before the introduction of the exogenous nucleic acid encoding the recombinant product of interest, or after the introduction of the exogenous nucleic acid encoding the recombinant product of interest.

In certain examples, the reduction of gene expression in the modified mammalian cells of the present disclosure is mediated by RNA silencing. In certain examples, the RNA silencing is selected from the group consisting of siRNA gene targeting and knockdown, shRNA gene targeting and knockdown, and miRNA gene targeting and knockdown.

In certain examples, the modified cells expressing a recombinant product of interest exhibit reduced or eliminated expression of:

WHAT IS CLAIMED IS:

1. A modified mammalian cell, wherein the expression of the expression products selected from the following groupings:
 - a) BAX; BAK; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
 - 5 b) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPL, LPLA2; and PPT1;
 - c) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and PPT1;
 - d) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
 - 10 e) BAX; BAK; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
 - f) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
 - g) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
 - h) BAX; BAK; ICAM-1; LPL; LPLA2; and PPT1;
 - 15 i) BAX; BAK; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
 - j) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
 - k) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and LIPA;
 - l) BAX; BAK; ICAM-1; SIRT-1; and MYC;
 - m) BAX; BAK; ICAM-1; PERK; SIRT-1; and MYC;
 - 20 n) BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
 - o) BAX; BAK; LPL; LPLA2; GGTA1; and CMAH;
 - p) BAX; BAK; PERK; LPL; LPLA2; GGTA1; and CMAH;
 - q) BAX; BAK; MYC; LPL; LPLA2; GGTA1; and CMAH;
 - 25 r) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
 - s) BAX; BAK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 - t) BAX; BAK; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 - u) BAX; BAK; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 - v) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 - 30 w) BAX; BAK; ICAM-1; and SIRT-1;
 - x) BAX; BAK; and ICAM-1;
 - y) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
 - z) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;

- aa) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- bb) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- 5 cc) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- dd) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- ee) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- 10 ff) BAX; BAK; BCKDHA; ICAM-1; LPL; LPLA2; and PPT1;
- gg) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
- hh) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
- ii) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and LIPA;
- 15 jj) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; and MYC;
- kk) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; and MYC;
- ll) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- mm) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; and CMAH;
- 20 nn) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; and CMAH;
- oo) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; and CMAH;
- pp) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
- qq) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- rr) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- 25 ss) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- tt) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- uu) BAX; BAK; BCKDHA; ICAM-1; and SIRT-1;
- vv) BAX; BAK; BCKDHA; and ICAM-1;
- 30 ww) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- xx) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;

yy) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL;
LPLA2; and PPT1;

zz) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL,
LPLA2; PPT1; and LIPA;

5 aaa) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPLA2; PPT1;
 and LIPA;

bbb) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH;
 LPLA2; PPT1; and LIPA;

ccc) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH;
10 LPLA2; PPT1; and LIPA;

ddd) BAX; BAK; BCKDHB; ICAM-1; LPL; LPLA2; and PPT1;

eee) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;

fff) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;

ggg) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2;
15 PPT1; and LIPA;

hhh) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; and MYC;

iii) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; and MYC;

jjj) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH;
 LPL, LPLA2; PPT1; and LIPA;

20 kkk) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;

lll) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;

mmm) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; and CMAH;

nnn) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
 CMAH;

25 ooo) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; CMAH; and PPT1;

ppp) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; CMAH; and
 PPT1;

qqq) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;

rrr) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
30 PPT1;

sss) BAX; BAK; BCKDHB; ICAM-1; and SIRT-1;

ttt) BAX; BAK; BCKDHB; and ICAM-1;

uuu) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
 LPL; LPLA2; and PPT1;

vvv) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPL; LPLA2; and PPT1;

www) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL; LPLA2; and PPT1;

5 xxx) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;

yyy) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
LPLA2; PPT1; and LIPA;

zzz) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
10 CMAH; LPLA2; PPT1; and LIPA;

aaaa) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPLA2; PPT1; and LIPA;

bbbb) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; LPL; LPLA2; and
PPT1;

15 cccc) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; LPL, LPLA2;
and PPT1;

dddd) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
LPLA2; and PPT1;

eeee) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
20 LPLA2; PPT1; and LIPA;

ffff) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; and MYC;

gggg) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1; and
MYC;

hhhh) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1;
25 MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;

iiii) BAX; BAK; BCKDHA; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;

jjjj) BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;

kkkk) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
and CMAH;

30 llll) BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
CMAH;

mmmm) BAX; BAK; BCKDHA; BCKDHB; LPL;
LPLA2; GGTA1; CMAH; and PPT1;

- nnnn) BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1;
CMAH; and PPT1;
- oooo) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
CMAH; and PPT1;
- 5 pppp) BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2;
GGTA1; CMAH; and PPT1;
- qqqq) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; and SIRT-1; or
- rrrr) BAX; BAK; BCKDHA; BCKDHB; and ICAM-1
- is reduced or eliminated relative to the expression of the endogenous products in an
- 10 unmodified cell.
2. The modified mammalian cell of claim 1, wherein:
- (a) the modified mammalian cell is transfected to express a recombinant product of interest; or
- (b) the modified mammalian cell is generated from a recombinant cell that expresses a
- 15 recombinant product of interest.
3. The modified mammalian cell of claim 1 or 2, wherein the selected grouping of expression products have no detectable expression.
4. The modified mammalian cell of claim 2, wherein the recombinant product of interest comprises a recombinant protein encoded by an exogenous nucleic acid sequence.
- 20 5. The modified mammalian cell of claim 4, wherein the recombinant protein is antibody or an antigen-binding fragment thereof.
6. The modified mammalian cell of claim 4, wherein the exogenous nucleic acid sequence is integrated in the cellular genome of the mammalian cell at one or more targeted locations.
- 25 7. The modified mammalian cell of any one of claims 1-6, wherein the modified cell does not express detectable BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPLA2; PPT1; BCKDHA; BCKDHB; LPL; and/or LIPA.

8. The modified mammalian cell of any one of claims 1-7, wherein the modified cell is a modified CHO cell, a modified HEK 293, a modified HEK 293T cell, a modified BHK cell, a modified A549 cell, or a modified HeLa cell.
9. A composition comprising the modified mammalian cell of any one of claims 1-8.
- 5 10. A method of producing a recombinant product of interest comprising:
 - i) culturing the modified mammalian cell of any one of claims 1-8;
 - ii) recovering the recombinant product of interest from the cultivation medium or the modified mammalian cells.
11. A method for producing a modified mammalian cell, comprising:
 - 10 (1) applying a nuclease-assisted and/or nucleic acid targeting at least one endogenous gene selected from the group of genes consisting of
 - a) BAX; BAK; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
 - b) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
 - c) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and
 - 15 PPT1;
 - d) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
 - e) BAX; BAK; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
 - f) BAX; BAK; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
 - 20 g) BAX; BAK; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
 - h) BAX; BAK; ICAM-1; LPL; LPLA2; and PPT1;
 - i) BAX; BAK; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
 - j) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
 - 25 k) BAX; BAK; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and LIPA;
 - l) BAX; BAK; ICAM-1; SIRT-1; and MYC;
 - m) BAX; BAK; ICAM-1; PERK; SIRT-1; and MYC;
 - n) BAX; BAK; ICAM-1; SIRT-1; PERK; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
 - 30 o) BAX; BAK; LPL; LPLA2; GGTA1; and CMAH;

- p) BAX; BAK; PERK; LPL; LPLA2; GGTA1; and CMAH;
- q) BAX; BAK; MYC; LPL; LPLA2; GGTA1; and CMAH;
- r) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
- s) BAX; BAK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- 5 t) BAX; BAK; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- u) BAX; BAK; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- v) BAX; BAK; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
- w) BAX; BAK; ICAM-1; and SIRT-1;
- x) BAX; BAK; and ICAM-1;
- 10 y) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- z) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- aa) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL; LPLA2; and PPT1;
- 15 bb) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- cc) BAX; BAK; BCKDHA; ICAM-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- dd) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- 20 ee) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPLA2; PPT1; and LIPA;
- ff) BAX; BAK; BCKDHA; ICAM-1; LPL; LPLA2; and PPT1;
- gg) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; LPL, LPLA2; and PPT1;
- hh) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
- 25 ii) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; MYC; LPL; LPLA2; PPT1; and LIPA;
- jj) BAX; BAK; BCKDHA; ICAM-1; SIRT-1; and MYC;
- kk) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; and MYC;
- ll) BAX; BAK; BCKDHA; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;
- 30 mm) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; and CMAH;
- nn) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; and CMAH;
- oo) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; and CMAH;

pp) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; and CMAH;
 qq) BAX; BAK; BCKDHA; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 rr) BAX; BAK; BCKDHA; PERK; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 ss) BAX; BAK; BCKDHA; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;
 5 tt) BAX; BAK; BCKDHA; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
 PPT1;
 uu) BAX; BAK; BCKDHA; ICAM-1; and SIRT-1;
 vv) BAX; BAK; BCKDHA; and ICAM-1;
 ww) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPL; LPLA2;
 10 and PPT1;
 xx) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH; LPL; LPLA2; and
 PPT1;
 yy) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL;
 LPLA2; and PPT1;
 15 zz) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH; LPL,
 LPLA2; PPT1; and LIPA;
 aaa) BAX; BAK; BCKDHB; ICAM-1; GGTA1; CMAH; LPLA2; PPT1;
 and LIPA;
 bbb) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; GGTA1; CMAH;
 20 LPLA2; PPT1; and LIPA;
 ccc) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; GGTA1; CMAH;
 LPLA2; PPT1; and LIPA;
 ddd) BAX; BAK; BCKDHB; ICAM-1; LPL; LPLA2; and PPT1;
 eee) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; LPL; LPLA2; and PPT1;
 25 fff) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2; and PPT1;
 ggg) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; MYC; LPL; LPLA2;
 PPT1; and LIPA;
 hhh) BAX; BAK; BCKDHB; ICAM-1; SIRT-1; and MYC;
 iii) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; and MYC;
 30 jjj) BAX; BAK; BCKDHB; ICAM-1; PERK; SIRT-1; MYC; GGTA1; CMAH;
 LPL; LPLA2; PPT1; and LIPA;
 kkk) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;
 ll) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;
 mmm) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; and CMAH;

nnn) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
CMAH;

ooo) BAX; BAK; BCKDHB; LPL; LPLA2; GGTA1; CMAH; and PPT1;

ppp) BAX; BAK; BCKDHB; PERK; LPL; LPLA2; GGTA1; CMAH; and
5 PPT1;

qqq) BAX; BAK; BCKDHB; MYC; LPL; LPLA2; GGTA1; CMAH; and PPT1;

rrr) BAX; BAK; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; CMAH; and
PPT1;

sss) BAX; BAK; BCKDHB; ICAM-1; and SIRT-1;

10 ttt) BAX; BAK; BCKDHB; and ICAM-1;

uuu) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
LPL; LPLA2; and PPT1;

vvv) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPL; LPLA2; and PPT1;

15 www) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL; LPLA2; and PPT1;

xxx) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPL; LPLA2; PPT1; and LIPA;

yyy) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; GGTA1; CMAH;
20 LPLA2; PPT1; and LIPA;

zzz) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; GGTA1;
CMAH; LPLA2; PPT1; and LIPA;

aaaa) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC;
GGTA1; CMAH; LPLA2; PPT1; and LIPA;

25 bbbb) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; LPL; LPLA2; and
PPT1;

cccc) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; LPL; LPLA2;
and PPT1;

dddd) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
30 LPLA2; and PPT1;

eeee) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; MYC; LPL;
LPLA2; PPT1; and LIPA;

ffff) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; SIRT-1; and MYC;

gggg) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1; and
MYC;

hhhh) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; PERK; SIRT-1;
MYC; GGTA1; CMAH; LPL, LPLA2; PPT1; and LIPA;

5 iii) BAX; BAK; BCKDHA; BCKDHB; LPL; LPLA2; GGTA1; and CMAH;
jjjj) BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1; and CMAH;

kkkk) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
and CMAH;

llll) BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2; GGTA1; and
10 CMAH;

mmmm) BAX; BAK; BCKDHA; BCKDHB; LPL;
LPLA2; GGTA1; CMAH; and PPT1;

nnnn) BAX; BAK; BCKDHA; BCKDHB; PERK; LPL; LPLA2; GGTA1;
CMAH; and PPT1;

15 oooo) BAX; BAK; BCKDHA; BCKDHB; MYC; LPL; LPLA2; GGTA1;
CMAH; and PPT1;

pppp) BAX; BAK; BCKDHA; BCKDHB; MYC; PERK; LPL; LPLA2;
GGTA1; CMAH; and PPT1;

qqqq) BAX; BAK; BCKDHA; BCKDHB; ICAM-1; and SIRT-1; or

20 rrrr) BAX; BAK; BCKDHA; BCKDHB; and ICAM-1
in the mammalian cell to reduce or eliminate the expression of said endogenous
gene, and

(2) selecting the modified mammalian cell wherein the expression of said
endogenous genes has been reduced or eliminated as compared to an
25 unmodified mammalian cell.

12. The method according to claim 11, wherein the modification is performed before the
introduction of the exogenous nucleic acid encoding the recombinant product of interest,
or after the introduction of the exogenous nucleic acid encoding the recombinant product
of interest.

30 13. The method according to any one of claims 10-12, wherein the reduction of gene
expression is mediated by RNA silencing.

14. The method of any one of claims 10 or 12-13, wherein the recombinant product of interest is encoded by a nucleic acid sequence.
15. The method of claim 14, wherein the nucleic acid sequence is integrated in the cellular genome of the modified cells at one or more targeted locations.
- 5 16. The method of claim 14, wherein the nucleic acid sequence is randomly integrated in the cellular genome of the mammalian cells.
17. The method of any one of claims 10, 12-13, or 14-16, wherein the recombinant product of interest comprises a viral vector or a viral particle.
18. The method of any one of claims 10, 12-13, or 14-17, wherein the recombinant
10 product of interest comprises a recombinant protein.
19. The method of claim 18, wherein the recombinant protein is an antibody or an antigen-binding fragment thereof.
20. The method of any one of claims 10, 12-13, or 14-19, comprising purifying the
15 product of interest, harvesting the product of interest, and/or formulating the product of interest.
21. The method of any one of claims 10, 12-13, or 14-20, wherein the modified mammalian cell is a modified CHO cell, a modified HEK 293 cell, a modified HEK 293T cell, a modified BHK cell, a modified A549 cell, or a modified HeLa cell.