CLAIMS

What Is Claimed Is:

1. A method of cell culture, the method comprising

(i) culturing mammalian cells in a cell culture medium,

(ii) measuring the concentration of at least one metabolite, and

(iii) maintaining the at least one metabolite below an inhibitory concentration in the cell culture medium for the at least one metabolite by increasing enzyme expression to reduce synthesis of the at least one metabolite when the measured concentration of the at least one metabolite is above a predefined value,

wherein the at least one metabolite includes aconitic acid (AA), leucinic acid (HICA), cytidine monophosphate (CMP), methylsuccinic acid (MSA), trigonelline (TRI), N-acetylputrescinium (NAP), or combinations thereof, and

wherein the enzyme comprises alcohol dehydrogenase 5 (ADH5), branched-chain amino acid transaminase 1 (BCAT1), or combinations thereof.

2. The method of claim 1, wherein the enzyme further comprises glutamic oxaloacetic transaminase 1 (GOT1), hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta (HADHB), 4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1), solute carrier family 35 member A1 (SLC35A1), catalase (CAT), or combinations thereof.

3. The method of claim 1, wherein increasing enzyme expression to reduce the synthesis of the metabolite comprises adding a recombinant deoxyribonucleic acid (DNA) molecule to overexpress the enzyme, wherein the enzyme is a downstream enzyme.

4. The method of claim 1, wherein:

the at least one metabolite includes HICA and the enzyme to reduce the synthesis of HICA comprises ADH5, BCAT1, solute carrier family 35 member A1 (SLC35A1), glutamic oxaloacetic transaminase 1 (GOT1), hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta (HADHB), or combinations thereof;

the at least one metabolite includes CMP and the enzyme to reduce the synthesis of CMP comprises ADH5, BCAT1, catalase (CAT), GOT1, HOGA1, SLC35A1, HADHB or combinations thereof;

the at least one metabolite includes MSA and the enzyme to reduce the synthesis of MSA comprises BCAT1, GOT1, HADHB, HOGA1, SLC35A1 or combinations thereof;

the at least one metabolite includes TRI and the enzyme to reduce the synthesis of TRI comprises BCAT1, GOT1, HADHB, CAT, HOGA1, SLC35A1, or combinations thereof;

the at least one metabolite includes NAP and the enzyme to reduce the synthesis of NAP comprises BCAT1, SLC35A1, HOGA1, GOT1, CAT, HADHB or combinations thereof;

the at least one metabolite includes trans-aconitic acid and the enzyme to reduce the synthesis of trans-aconitic acid is BCAT1, ADH5, GOT1, HOGA1, SLC35A1, HADHB, or combinations thereof; or

combinations thereof.

5. The method of claim 1, wherein the enzyme comprises ADH5, BCAT1, glutamic oxaloacetic transaminase 1 (GOT1), hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta (HADHB), 4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1), solute carrier family 35 member A1 (SLC35A1), and catalase (CAT).

6. The method of claim 1, wherein the concentration of the at least one metabolite is measured using nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy, High/Ultra Performance Liquid Chromatography (H/UPLC), Liquid Chromatography Mass Spectrometer (LC-MS), Gas Chromatography Mass Spectrometer (GC-MS) technology, or combinations thereof.

7. The method of claim 1, wherein maintaining the at least one metabolite below an inhibitory concentration in the cell culture medium for the at least one metabolite comprises controlling temperature, dissolved oxygen level, pH, or combinations thereof.

8. The method of claim 1, wherein the mammalian cells are CHO cells, HEK 293 cells, HT-1080 cells, engineered T cells, or engineered natural killer cells.

9. The method of claim 1, wherein the cell culture is a batch culture, a fed batch culture, or a perfusion culture.

10. The method of claim 1, wherein the mammalian cells express a recombinant protein, a gene product, or a cell product.

11. The method of claim 10, wherein the recombinant protein is a monoclonal antibody.

12. The method of claim 1, wherein cell growth and/or productivity are increased as compared to a control culture, wherein the control culture is identical to the culture of claim 1 except it is not cultured using step (iii).

13. The method of claim 12, wherein the cell growth is determined by maximum viable

cell density and is increased by at least 5% as compared to the control culture.

14. The method of claim 1, wherein:

the at least one metabolite includes AA and concentration of AA in the cell culture medium is maintained lower than 440 μM,

the at least one metabolite includes HICA and concentration of HICA in the cell culture medium is maintained lower than 23.5 μM,

the at least one metabolite includes CMP and concentration of CMP in the cell culture medium is maintained lower than 10 μM,

the at least one metabolite includes MSA and concentration of MSA in the cell culture medium is maintained lower than 3.75 μM,

the at least one metabolite includes TRI and concentration of TRI in the cell culture medium is maintained lower than 0.35 μM,

the at least one metabolite includes NAP and concentration of NAP in the cell culture medium is maintained lower than 0.3 μM, or

combinations thereof.

15. The method of claim 14, wherein the concentration of the at least one metabolite is measured using nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy, High/Ultra Performance Liquid Chromatography (H/UPLC), Liquid Chromatography Mass Spectrometer (LC-MS), Gas Chromatography Mass Spectrometer (GC-MS) technology, or combinations thereof.