CLAIMS

1. A method of selecting a eukaryotic cell comprising a nucleic acid sequence encoding a product of interest, the method comprising:

i) contacting a population of cells that are unable to survive or grow in the absence of tyrosine, with a vector system comprising

a) a first nucleic acid sequence comprising a sequence encoding a phenylalanine hydroxylase (PAH) which lacks a functional N-terminal regulatory domain, operably linked to a first control sequence which enables expression of the PAH in a host cell;

(b) a second nucleic acid sequence comprising a sequence encoding a GTP cyclohydrolase 1 (GCH1) operably linked to a second control sequence which enables expression of the GCH1 in a host cell; and

(c) a third nucleic acid sequence comprising a sequence encoding a product of interest operably linked to a third control sequence which enables expression of the product in a host cell, which third sequence is present in the same vector as (a) and/or (b), under conditions that permit uptake of the vector system by the cells;

ii) culturing the cells under conditions where the level of tyrosine is lower than the level required for survival or growth of cells that do not express the PAH and GCH1 enzymes encoded by the vector system; and

iii) selecting one or more cells that are able to grow under such conditions to obtain one or more cells which contain the nucleic acid sequence encoding the product.

2. A method according to claim 1 wherein (a), (b) and (c) are present in the same vector.

3. A method according to claim 1 or claim 2 comprising two vectors wherein (c) is present in the same vector as (a) or (b).

4. A method according to any one of claims 1 to 3 wherein the eukaryotic cell is a mammalian cell, for example a CHO cell.

5. A host cell according to any one of the preceding wherein the PAH has a deletion of the N-terminal regulatory domain.

6. A method according to any one of the preceding claims wherein the cell culture medium lacks tyrosine and is optionally supplemented with phenylalanine.

7. A eukaryotic host cell comprising:

a) a first exogenous nucleic acid comprising a sequence which encodes a phenylalanine hydroxylase (PAH) which lacks a functional N-terminal regulatory domain, operably linked to a first control sequence which enables expression of the PAH in the host cell; and

b) a second exogenous nucleic acid which encodes a GTP cyclohydrolase 1 (GCH1), operably linked to a second control sequence which enables expression of the GCH1 in the host cell; and

c) a third exogenous nucleic acid which encodes a product of interest, operably linked to a third control sequence which enables expression of the product in the host cell, which third exogenous nucleic acid is present in the same exogenous nucleic acid sequence as the first and/or second exogenous nucleic acid.

8. A host cell according to claim 7 wherein the PAH has a deletion of the N-terminal regulatory domain.

9. A host cell according to claim 7 or claim 8 wherein the PAH is CHO or human PAH.

10. A host cell according to any one of claims 7 to 9 which is a mammalian cell, for example a CHO cell.

11. A host cell according to any one of claims 7 to 10 wherein the first, second and third nucleic acid molecules are integrated into the genome of the host cell.

12. A host cell according to any one of claims 7 to 10 wherein the activity of the cell's endogenous genes encoding PAH and/or GCH1 has been reduced or abolished.

13. A vector system comprising one or more nucleic acid vectors comprising:

a) a first nucleic acid sequence comprising a sequence encoding a phenylalanine hydroxylase (PAH) which lacks a functional N-terminal regulatory domain, operably linked to a first control sequence which enables expression of the PAH in a host cell;

b) a second nucleic acid sequence comprising a sequence encoding a GTP cyclohydrolase 1 (GCH1) operably linked to a second control sequence which enables expression of the GCH1 in a host cell; and

c) a multiple cloning site for inserting a sequence encoding a product of interest operably linked to a third control sequence which enables expression of the product in a host cell, wherein the multiple cloning site and third control sequence are present in the same vector as (a) and/or (b).

14. A vector system comprising one or more nucleic acid vectors comprising:

a) a first nucleic acid sequence comprising a sequence encoding a phenylalanine hydroxylase (PAH) which lacks a functional N-terminal regulatory domain, operably linked to a first control sequence which enables expression of the PAH in a host cell;

b) a second nucleic acid sequence comprising a sequence encoding a GTP cyclohydrolase 1 (GCH1) operably linked to a second control sequence which enables expression of the GCH1 in a host cell; and

c) a third nucleic acid sequence comprising a sequence encoding a product of interest operably linked to a third control sequence which enables expression of the product in a host cell, which third nucleic acid sequence is present in the same vector as (a) and/or (b).

15. A method of making a product, the method comprising culturing a host cell according to any one of claims 7 to 10 under conditions suitable for expressing the product, and recovering the product, and optionally subjecting the recovered product to one or more treatment or purification steps.

16. A method according to claim 15, wherein the cells are cultured under conditions where the level of tyrosine is lower than the level required for survival or growth of cells that do not express the PAH and GCH1 enzymes encoded by the vector system defined in any one of claims 1 to 5.