

CLAIMS

1. A genetically engineered bacterium comprising:
 - (a) one or more gene(s) encoding a phenylalanine ammonia lyase (PAL), in which the gene(s) encoding a PAL is operably linked to a directly or indirectly inducible promoter that is not associated with the PAL gene in nature; and
 - (b) one or more gene(s) encoding a phenylalanine transporter, in which the gene(s) encoding the phenylalanine transporter is operably linked to a directly or indirectly inducible promoter that is not associated with the phenylalanine transporter gene in nature.
2. A genetically engineered bacterium according to Claim 1, further comprising one or more gene(s) encoding an L-aminoacid deaminase (LAAD), in which the gene(s) encoding LAAD is operably linked to a directly or indirectly inducible promoter that is not associated with the LAAD gene in nature.
3. A genetically engineered bacterium according to Claim 1 or 2, in which the promoter operably linked to the gene(s) encoding the PAL and the promoter operably linked to the gene(s) encoding the phenylalanine transporter are separate copies of the same promoter.
4. A genetically engineered bacterium according to Claim 1 or 2, in which the gene(s) encoding the PAL and the gene(s) encoding the phenylalanine transporter are operably linked to the same copy of the same promoter.
5. A genetically engineered bacterium according to Claim 2, 3 or 4, in which the gene(s) encoding the LAAD is operably linked to a different promoter from that of the gene(s) encoding the PAL and the gene(s) encoding the phenylalanine transporter.
6. A genetically engineered bacterium according to any preceding claim, in which the promoter or promoters operably linked to the gene(s) encoding the PAL and the gene(s) encoding the phenylalanine transporter are directly or indirectly induced under low-oxygen or anaerobic conditions.
7. A genetically engineered bacterium according to any preceding claim, in which the promoter or promoters operably linked to the gene(s) encoding the PAL and the gene(s) encoding the phenylalanine transporter are selected from the group consisting of an FNR-responsive promoter, an ANR-responsive promoter, and a DNR-responsive promoter.

8. A genetically engineered bacterium according to Claim 5, 6 or 7, in which the gene(s) encoding the PAL and the gene(s) encoding the phenylalanine transporter are operably linked to the same copy of the same promoter.
9. A genetically engineered bacterium according to any of Claims 2 to 7, in which the gene encoding the LAAD is under the control of a promoter that is directly or indirectly induced by low oxygen conditions.
10. A genetically engineered bacterium according to any of Claims 2 to 7, in which the gene encoding the LAAD is under the control of a promoter that is directly or indirectly induced by arabinose or tetracycline.
- 10 11. A genetically engineered bacterium according to any preceding claim, in which the gene(s) encoding the phenylalanine transporter is located on a chromosome in the bacterium.
12. A genetically engineered bacterium according to any of Claims 1 to 10, in which the gene(s) encoding the phenylalanine transporter is located on a plasmid in the bacterium.
13. A genetically engineered bacterium according to any preceding claim, in which the gene(s) encoding the PAL is located on a plasmid in the bacterium.
- 15 14. A genetically engineered bacterium according to any of Claims 1 to 12, in which the gene(s) encoding the PAL is located on a chromosome in the bacterium.
15. A genetically engineered bacterium according to any preceding claim, in which the PAL is from *Anabaena variabilis* (PAL1) or from *Photorhabdus luminescens* (PAL3).
- 20 16. A genetically engineered bacterium according to any preceding claim, in which the phenylalanine transporter is PheP.
17. A genetically engineered bacterium according to any preceding claim, in which the engineered bacterium comprises 1-5 copies of a gene(s) encoding the PAL, 1-5 copies of a gene(s) encoding the phenylalanine transporter, and optionally 1-5 copies of gene(s) encoding the LAAD.
- 25 18. A genetically engineered bacterium according to any preceding claim, in which the bacterium is a probiotic bacterium.

19. A genetically engineered bacterium according to Claim 18, in which the bacterium is selected from the group consisting of *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Escherichia*, *Lactobacillus*, and *Lactococcus*.
20. A genetically engineered bacterium according to Claim 19, in which the bacterium is
5 *Escherichia coli* strain Nissle.
21. A genetically engineered bacterium according to any preceding claim, in which the bacterium is an auxotroph in a gene that is complemented when the bacterium is present in a mammalian gut.
22. A genetically engineered bacterium according to Claim 21, in which the mammalian gut
10 is a human gut.
23. A genetically engineered bacterium according to Claim 21 or 22, in which the bacterium is an auxotroph in diaminopimelic acid or an enzyme in the thymidine biosynthetic pathway.
24. A genetically engineered bacterium according to any of Claims 1 to 21, in which the bacterium is further engineered to harbor a gene encoding a substance toxic to the bacterium.
- 15 25. A genetically engineered bacterium according to Claim 24, in which the gene encoding the substance toxic to the bacterium is operably linked to a directly or indirectly inducible promoter.
26. A pharmaceutically acceptable composition comprising a bacterium according to any preceding claim; and a pharmaceutically acceptable carrier.
- 20 27. A composition according to Claim 26 formulated for oral administration.
28. Use of a composition according to Claim 26 or 27 in the manufacture of a medicament for reducing hyperphenylalaninemia or treating a disease associated with hyperphenylalaninemia.
29. Use according to Claim 28, in which the disease is selected from the group consisting
25 of: phenylketonuria, classical or typical phenylketonuria, atypical phenylketonuria, permanent mild hyperphenylalaninemia, nonphenylketonuric hyperphenylalaninemia, phenylalanine hydroxylase deficiency, cofactor deficiency, dihydropteridine reductase deficiency, tetrahydropterin synthase deficiency, Segawa's disease, and liver disease.