CLAIMS

We claim:

1. An engineered phenylalanine ammonia lyase polypeptide comprising an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 6, wherein said amino acid sequence of said engineered polypeptide comprises an amino acid residue difference at position 16, wherein the amino acid positions of said amino acid sequence of said engineered polypeptide are numbered with reference to the amino acid sequence of SEQ ID NO:2.

2. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein the amino acid sequence of said engineered polypeptide further comprises at least one substitution or substitution set at one or more amino acid positions selected from 150, 44/56, 44/56/102/239/285/469/470/495, 44/239, 44/239/285/469/495, 44/239/285/470, 44/239/469/470, 44/239/470/546, 44/239/495, 44/239/495/546, 44/469/470, 102, 102/470, 162, 165, 188, 239/285, 239/285/469, 239/469/470/495, 264, 267, 285/469/470/495, 285/470, 285/470/495, 364, 455, 469/470, 472, and 482, wherein the amino acid positions are numbered with reference to SEQ ID NO:6.

3. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein the amino acid sequence of said engineered polypeptide further comprises at least one substitution at one or more amino acid positions selected from 264, 364, 472, 482, and/or any combinations thereof, wherein the amino acid positions are numbered with reference to SEQ ID NO:6.

4. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein the amino acid sequence of said engineered polypeptide further comprises at least one substitution at one or more amino acid positions selected from 150, 162, 188, 264, 267, 398, 434, 472, and 482, and/or any combinations thereof, wherein the amino acid positions are numbered with reference to SEQ ID NO:6.

5. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein said engineered polypeptide is an *Anabaena variabilis* variant enzyme.

6. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein said engineered polypeptide is more thermostable than wild-type *Anabaena variabilis* phenylalanine ammonia lyase.

7. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein said

engineered polypeptide is more resistant to proteolysis than wild-type *Anabaena variabilis* phenylalanine ammonia lyase.

8. The engineered phenylalanine ammonia lyase polypeptide of Claim 7, wherein said engineered phenylalanine ammonia lyase polypeptide is resistant to proteolysis by at least one digestive tract enzyme, than wild-type *Anabaena variabilis* phenylalanine ammonia lyase.

9. The engineered phenylalanine ammonia lyase polypeptide of Claim 7, wherein said engineered phenylalanine ammonia lyase polypeptide is more resistant to proteolysis by chymotrypsin, trypsin, carboxypeptidases, and/or elastases than wild-type *Anabaena variabilis* phenylalanine ammonia lyase.

10. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein said engineered polypeptide is more acid stable than wild-type *Anabaena variabilis* phenylalanine ammonia lyase.

11. The engineered phenylalanine ammonia lyase polypeptide of Claim 1, wherein said polypeptide is purified.

12. A composition comprising at least one engineered phenylalanine ammonia lyase polypeptide of Claim 1.

13. The composition of Claim 12, wherein said composition is a pharmaceutical composition.

14. The composition of Claim 13, further comprising at least one pharmaceutically acceptable excipient and/or carrier.

15. The composition of Claim 13, wherein said composition is suitable for the treatment of phenylketonuria.

16. The composition of Claim 13, wherein said composition is suitable for the treatment of elevated blood phenylalanine.

17. The composition of Claim 13, wherein said composition is suitable for the treatment of tyrosinemia.

18. The composition of Claim 13, wherein said composition is suitable for the treatment of elevated blood tyrosine.

19. The composition of Claim 13, wherein said composition is in the form of a pill, tablet, capsule, gelcap, liquid, or emulsion.

20. The composition of Claim 19, wherein said pill, tablet, capsule, or gelcap further comprises an enteric coating.

21. The composition of Claim 13, wherein said composition is suitable for parenteral injection into a human.

22. The composition of Claim 13, wherein said composition is suitable for coadministrationered with at least one additional therapeutically effective compound.

23. The composition of Claim 22, wherein said composition comprises at least one additional therapeutically effective compound.

24. Use of a composition according to Claim 13 in the manufacture of a medicament, said medicament being suitable for use in aA method for treating the symptoms of phenylketonuria in a subject, said method comprising providing a subject having phenylketonuria, and providing the composition of Claim 13, medicament to said subject.

25. The usemethod of Claim 24, wherein the medicament is capable of reducing the phenylalanine concentration in the blood of said subject is reduced upon providing said composition to said subject.

26. The usemethod of Claim 24, wherein the medicament is capable of reducing the cinnamic acid concentration in the blood of said subject is increased upon providing said composition to said subject.

27. Use of a composition according to Claim 13 in the manufacture of a medicament, said medicament being suitable for use in aA method for treating the symptoms of phenylketonuria in a subject, said method comprising providing a subject having phenylketonuria, and providing the composition of Claim 13,medicament to said subject, and wherein said subject is able to eat a diet that is less restricted in its phenylalanine content than diets required by subjects who have not been

provided said ~~composition~~medicament.

28. The use~~method~~ of Claim 27, wherein said subject is an infant, child, young adult, or adult.