WHAT IS CLAIMED IS:

1. A multimeric protein structure comprising at least two α-galactosidase monomers being covalently linked to one another via a linking moiety, the multimeric protein structure featuring a characteristic selected from the group consisting of:

(a) an α-galactosidase activity upon subjecting the multimeric protein structure to human plasma conditions for one hour, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(b) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to human plasma conditions for one hour by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(c) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to human plasma conditions for one hour;

(d) an α-galactosidase activity, upon subjecting the multimeric protein structure to lysosomal conditions for one week, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said lysosomal conditions for one week;

(e) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to lysosomal conditions for one day by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said lysosomal conditions for one day;

(f) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day;

(g) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to lysosomal conditions, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native form of said protein to said lysosomal conditions;

(h) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to an aqueous solution having a pH of 7 and a temperature of 37 °C, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native α-galactosidase to said aqueous solution having a pH of 7 and a temperature of 37 °C; and

(i) a circulating half-life in a physiological system which is higher by at least 20 % than said circulating half-life of said native α-galactosidase.

2. The multimeric protein structure of claim 1, wherein said α-galactosidase activity of said multimeric protein structure which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day, further remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one week.

3. The multimeric protein structure of any of claims 1 to 2, wherein said linking moiety is not present in native α-galactosidase.

4. A multimeric protein structure comprising at least two α-galactosidase monomers being covalently linked to one another via a linking moiety, wherein said linking moiety is not present in native α-galactosidase.

5. The multimeric protein structure of claim 4, featuring a characteristic selected from the group consisting of:

(a) an α-galactosidase activity, upon subjecting the multimeric protein structure to human plasma conditions for one hour, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(b) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to human plasma conditions for one hour by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(c) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to human plasma conditions for one hour;

(d) an α-galactosidase activity, upon subjecting the multimeric protein structure to lysosomal conditions for one week, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said lysosomal conditions for one week;

(e) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to lysosomal conditions for one day by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said lysosomal conditions for one day;

(f) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day;

(g) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to lysosomal conditions, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native α-galactosidase to said lysosomal conditions;

(h) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to an aqueous solution having a pH of 7 and a temperature of 37 °C, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native α-galactosidase to said aqueous solution having a pH of 7 and a temperature of 37 °C; and

(i) a circulating half-life in a physiological system which is higher than a circulating half-life of said native α-galactosidase.

6. The multimeric protein structure of claim 5, wherein said α-galactosidase activity of said multimeric protein structure which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day, further remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one week.

7. The multimeric protein structure of any of claims 5 and 6, wherein said circulating half-life of the multimeric protein structure which is higher than a circulating

half-life of said native α-galactosidase, is higher by at least 20 % than said circulating half-life of said native α-galactosidase.

8. The multimeric protein structure of claim 7, wherein said circulating half-life of the multimeric protein structure which is higher than a circulating half-life of said native α-galactosidase, is higher by at least 50 % than said circulating half-life of said native α-galactosidase.

9. The multimeric protein structure of any of claims 1 to 8, characterized by an α-galactosidase activity in an organ upon administration of said multimeric protein structure to a vertebrate, said organ being selected from the group consisting of a spleen, a heart and a kidney.

10. The multimeric protein structure of any of claims 1 to 9, comprising two α-galactosidase monomers, the protein structure being a dimeric protein structure.

11. The multimeric protein structure of any of claims 1 to 10, wherein said α-galactosidase is a human α-galactosidase.

12. The multimeric protein structure of any of claims 1 to 11, wherein said α-galactosidase is a recombinant α-galactosidase.

13. The multimeric protein structure of any of claims 1 to 11, wherein said α-galactosidase is a plant recombinant α-galactosidase.

14. The multimeric protein structure of any of claims 1 to 13, wherein said α-galactosidase has an amino acids sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3.

15. The multimeric protein structure of any of claims 1 to 13, wherein said α-galactosidase is an alkaline α-galactosidase.

16. The multimeric protein structure of any of claims 1 to 13, wherein said α-galactosidase is an acid α-galactosidase.

17. The multimeric protein structure of of any of claims 1 to 16, wherein said linking moiety is at least 20 atoms long.

18. The multimeric protein structure of any of claims 1 to 17, wherein said linking moiety comprises a poly(alkylene glycol).

19. The multimeric protein structure of claim 18, wherein said poly(alkylene glycol) comprises at least two functional groups, each functional group forming a covalent bond with one of the α-galactosidase monomers.

20. The multimeric protein structure of claim 19, wherein said at least two functional groups are terminal groups of said poly(alkylene glycol).

21. The multimeric protein structure of any of claims 1 to 16, wherein said at least one linking moiety has a general formula:

$$-X_1-(CR_1R_2-CR_3R_4-Y)n-X_2-$$

wherein each of X_1 and X_2 is a functional group that forms a covalent bond with at least one α-galactosidase monomer;

Y is O, S or NR_5;

n is an integer from 1 to 200; and

each of R_1, R_2, R_3, R_4 and R_5 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, hydroxy, oxo, thiol and thioalkoxy.

22. The multimeric protein structure of any of claims 19 to 21, wherein at least one of said functional groups forms an amide bond with an α-galactosidase monomer.

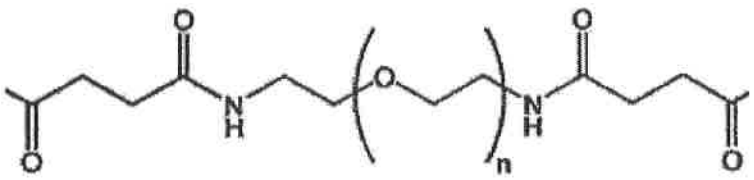
23. The multimeric protein structure of claim 21, wherein n is an integer from 5 to 150.

24. The multimeric protein structure of claim 21, wherein n is an integer from 40 to 70.

25. The multimeric protein structure of claim 21, wherein n is at least 25.

26. The multimeric protein structure of claim 21, comprising two α-galactosidase monomers, the protein structure being a dimeric protein structure, wherein said α-galactosidase has an amino acids sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3, each of said functional groups forms an amide bond with an α-galactosidase monomer, and n is an integer from 40 to 70.

27. The multimeric protein structure of claim 14, comprising two α-galactosidase monomers, the protein structure being a dimeric protein structure, wherein said linking moiety has the formula:



wherein a molecular weight of polyethylene glycol in said linking moiety is 2 kDa, and the terminal groups of said linking moiety each form an amide bond with an α-galactosidase monomer.

28. A process of preparing the multimeric protein structure of any of claims 1 to 27, the process comprising reacting α-galactosidase with a cross-linking agent which comprises said linking moiety and at least two reactive groups.

29. The process of claim 28, comprising reacting dimeric α-galactosidase with said cross-linking agent.

30. The process of any of claims 28 to 29, wherein said reactive groups comprise a leaving group.

31. The process of any of claims 28 to 30, wherein said reactive group reacts with an amine group to form an amide bond.

32. The process of any of claims 28 to 31, wherein each of said reactive groups is capable of forming a covalent bond between said linking moiety and at least one α-galactosidase monomer.

33. The process of any of claims 28 to 32, wherein a molar ratio of said cross-linking agent to monomers of said α-galactosidase is in a range of from 5:1 to 500:1.

34. The process of claim 33, wherein said molar ratio is in a range of from 75:1 to 300:1.

WHAT IS CLAIMED IS:

1. A multimeric protein structure comprising at least two α-galactosidase monomers being covalently linked to one another via a linking moiety, the multimeric protein structure featuring a characteristic selected from the group consisting of:

(a) an α-galactosidase activity upon subjecting the multimeric protein structure to human plasma conditions for one hour, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(b) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to human plasma conditions for one hour by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(c) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to human plasma conditions for one hour;

(d) an α-galactosidase activity, upon subjecting the multimeric protein structure to lysosomal conditions for one week, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said lysosomal conditions for one week;

(e) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to lysosomal conditions for one day by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said lysosomal conditions for one day;

(f) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day;

(g) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to lysosomal conditions, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native form of said protein to said lysosomal conditions;

(h) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to an aqueous solution having a pH of 7 and a temperature of 37 °C, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native α-galactosidase to said aqueous solution having a pH of 7 and a temperature of 37 °C; and

(i) a circulating half-life in a physiological system which is higher by at least 20 % than said circulating half-life of said native α-galactosidase.

2. The multimeric protein structure of claim 1, wherein said α-galactosidase activity of said multimeric protein structure which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day, further remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one week.

3. The multimeric protein structure of any of claims 1 to 2, wherein said linking moiety is not present in native α-galactosidase.

4. A multimeric protein structure comprising at least two α-galactosidase monomers being covalently linked to one another via a linking moiety, wherein said linking moiety is not present in native α-galactosidase.

5. The multimeric protein structure of claim 4, featuring a characteristic selected from the group consisting of:

(a) an α-galactosidase activity, upon subjecting the multimeric protein structure to human plasma conditions for one hour, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(b) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to human plasma conditions for one hour by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase

decreases upon subjecting said native α-galactosidase to said human plasma conditions for one hour;

(c) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to human plasma conditions for one hour;

(d) an α-galactosidase activity, upon subjecting the multimeric protein structure to lysosomal conditions for one week, which is at least 10 % higher than an activity of native α-galactosidase upon subjecting said native α-galactosidase to said lysosomal conditions for one week;

(e) an α-galactosidase activity which decreases upon subjecting the multimeric protein structure to lysosomal conditions for one day by a percentage which is at least 10 % less than the percentage by which an activity of said native α-galactosidase decreases upon subjecting said native α-galactosidase to said lysosomal conditions for one day;

(f) an α-galactosidase activity which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day;

(g) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to lysosomal conditions, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native α-galactosidase to said lysosomal conditions;

(h) an α-galactosidase activity, immediately upon subjecting the multimeric protein structure to an aqueous solution having a pH of 7 and a temperature of 37 °C, which is at least 10 % higher than an activity of native α-galactosidase immediately upon subjecting said native α-galactosidase to said aqueous solution having a pH of 7 and a temperature of 37 °C; and

(i) a circulating half-life in a physiological system which is higher than a circulating half-life of said native α-galactosidase.

6. The multimeric protein structure of claim 5, wherein said α-galactosidase activity of said multimeric protein structure which remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one day, further remains substantially unchanged upon subjecting the multimeric protein structure to lysosomal conditions for one week.

7. The multimeric protein structure of any of claims 5 and 6, wherein said circulating half-life of the multimeric protein structure which is higher than a circulating half-life of said native α-galactosidase, is higher by at least 20 % than said circulating half-life of said native α-galactosidase.

8. The multimeric protein structure of claim 7, wherein said circulating half-life of the multimeric protein structure which is higher than a circulating half-life of said native α-galactosidase, is higher by at least 50 % than said circulating half-life of said native α-galactosidase.

9. The multimeric protein structure of any of claims 1 to 8, characterized by an α-galactosidase activity in an organ upon administration of said multimeric protein structure to a vertebrate, said organ being selected from the group consisting of a spleen, a heart and a kidney.

10. The multimeric protein structure of any of claims 1 to 9, comprising two α-galactosidase monomers, the protein structure being a dimeric protein structure.

11. The multimeric protein structure of any of claims 1 to 10, wherein said α-galactosidase is a human α-galactosidase.

12. The multimeric protein structure of any of claims 1 to 11, wherein said α-galactosidase is a plant recombinant α-galactosidase.

13. The multimeric protein structure of any of claims 1 to 12, wherein said α-galactosidase has an amino acids sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3.

14. The multimeric protein structure of any of claims 1 to 12, wherein said α-galactosidase is an alkaline α-galactosidase.

15. The multimeric protein structure of any of claims 1 to 12, wherein said α-galactosidase is an acid α-galactosidase.

16. The multimeric protein structure of any of claims 1 to 15, wherein said linking moiety comprises a poly(alkylene glycol).

17. The multimeric protein structure of claim 16, wherein said poly(alkylene glycol) comprises at least two functional groups, each functional group forming a covalent bond with one of the α-galactosidase monomers.

18. The multimeric protein structure of claim 17, wherein said at least two functional groups are terminal groups of said poly(alkylene glycol).

19. The multimeric protein structure of any of claims 1 to 15, wherein said at least one linking moiety has a general formula:

$$-X_1-(CR_1R_2-CR_3R_4-Y)n-X_2-$$

wherein each of X_1 and X_2 is a functional group that forms a covalent bond with at least one α-galactosidase monomer;

Y is O, S or NR_5;

n is an integer from 1 to 200; and

each of R_1, R_2, R_3, R_4 and R_5 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, hydroxy, oxo, thiol and thioalkoxy.

20. The multimeric protein structure of any of claims 17 to 19, wherein at least one of said functional groups forms an amide bond with an α-galactosidase monomer.

21. The multimeric protein structure of claim 19, wherein n is an integer from 5 to 150.

22. The multimeric protein structure of claim 19, wherein n is an integer from 40 to 70.

23. A pharmaceutical composition comprising the multimeric protein structure of any of claims 1 to 22 and a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, further comprising a galactose.

25. The multimeric protein structure of any of claims 1 to 22, for use as a medicament.

26. The multimeric protein structure of claim 25, wherein said medicament is for treating Fabry disease.

27. The multimeric protein structure of any of claims 1 to 22, for use in treating Fabry disease.

28. A method of treating Fabry disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of the multimeric protein structure of any of claims 1 to 22, thereby treating the Fabry disease.

29. A process of preparing the multimeric protein structure of any of claims 1 to 22, the process comprising reacting α-galactosidase with a cross-linking agent which comprises said linking moiety and at least two reactive groups.

30. The process of claim 29, comprising reacting dimeric α-galactosidase with said cross-linking agent.

31. The process of any of claims 29 to 30, wherein said reactive groups comprise a leaving group.

32. The process of any of claims 29 to 31, wherein said reactive group reacts with an amine group to form an amide bond.

33. The process of any of claims 29 to 32, wherein each of said reactive groups is capable of forming a covalent bond between said linking moiety and at least one α-galactosidase monomer.

34. The process of any of claims 29 to 33, wherein a molar ratio of said cross-linking agent to monomers of said α-galactosidase is in a range of from 5:1 to 500:1.

35. The process of claim 34, wherein said molar ratio is in a range of from 75:1 to 300:1.