doses were disclosed which were within the range 0.001 mg to 100 mg or even higher and particularised dose ranges of 5 mg/kg to 100 mg/kg were noted. Only effects of rapamycin were exemplified. It is known that rapamycin use can lead to improvement of glucose control and diabetes.

As a result of studies performed by the Applicant, it has surprisingly been discovered that tacrolimus at a very low dose can be beneficial in treating adverse fat accumulation and associated conditions from that involved in immunosuppression. This is because at this very low dose range tacrolimus accesses a different mechanism in order to lead its newly discovered beneficial effects. It appears that this mechanism is not brought into play when higher doses of tacrolimus are employed.

Studies performed by the Applicant suggest that tacrolimus and its close structural analogues do not produce the beneficial effect described herein through any mechanism related to those which lead to immunosuppressant properties. Studies indicate that tacrolimus and its close structural analogues at certain specific concentrations acts by modulating certain genes. Without wishing to be limited to any mechanism of action, it is postulated that such epigenetic effects play a part in how tacrolimus acts to reduce adverse fat accumulation and/or treat sarcopenia and/or treat metabolic syndrome and its components. This appears to lead to different levels of oxidative enzymes which can lead to a reduction in oxidative stress.

Brief Summary ~~of the Invention~~

In one aspect of the present disclosure, there is provided tacrolimus or a close structural analogue thereof for use in treating a condition at a dose which does not cause immunosuppression and which produces a whole blood trough level of tacrolimus or its close structural analogue of at least 0.05 ng/mL, wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

In another aspect of the present disclosure, there is provided the use of tacrolimus or a close structural analogue thereof in the manufacture of a medicament for treating a condition which medicament does not cause immunosuppression and which produces a whole blood trough level of tacrolimus or its close structural analogue of at least 0.05 ng/mL, wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

In a further aspect of the present disclosure, there is provided tacrolimus or a close structural analogue thereof for use in treating one or more conditions where tacrolimus or its close structural analogue is administered not more than once a day at a dose of 0.007 mg/kg to 0.03 mg/kg and wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

In another aspect of the present disclosure, there is provided the use of tacrolimus of a close structural analogue thereof for the manufacture of a medicament for the treatment of one or more conditions by administration not more than once a day wherein the medicament comprises 0.007 mg/kg to 0.03 mg/kg and where the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;

(v) high triglycerides; or
(vi) metabolic syndrome.

In a further aspect of the present disclosure, there is provided tacrolimus or a close structural analogue for use in treating one or more conditions by administration once a day of an amount which effects genetic modification which leads to a reduction in oxidative stress wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

In another aspect of the present disclosure, there is provided the use of tacrolimus or a close structural analogue in the manufacture of a medicament for the treatment of one or more conditions by administration not more than once a day which medicament contains an amount of tacrolimus or a close structural analogue thereof which effects epigenetic modification which leads to a reduction in oxidative stress and wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

In a further aspect of the present disclosure, there is provided a unit dose pharmaceutical composition which comprises 0.05 mg to 0.8 mg of tacrolimus or a close structural analogue thereof for use in the treatment of one or more of:

(i) adverse fat accumulation;

(ii) sarcopenia;

(iii) hyperglycaemia or type II diabetes;

(iv) high cholesterol;

(v) high triglycerides; or

(vi) metabolic syndrome.

The present ~~invention~~ disclosure further provides a method of treatment of one or more conditions in a human in need thereof which comprises administering not more than once a day an effective amount of tacrolimus or a close structural analogue thereof which amount does not cause immunosuppression and which produces a whole blood trough level of tacrolimus or its close structural analogue of at least 0.05 ng/mL, wherein the one or more conditions is one or more of: (i)adverse fat accumulation; (ii) sarcopenia; (iii) hyperglycaemia or type II diabetes; (iv) high cholesterol; (v) high triglycerides; or (vi) metabolic syndrome.

Aptly the ~~invention~~ uses or methods disclosed herein employs once a day dose of 0.0007 mg/kg to 0.03 mg/kg of such agents.

The ~~invention~~ uses or methods disclosed herein can lead to a reduction in oxidative stress and/or epigenetic modification which can lead to loss in accumulated fat, a reduction in high cholesterol levels, a reduction in triglyceride levels and/or the other conditions set out above.

Description of the Figures

Figure 1 shows the extension on lifespan profile of S. Cerevisiae resulting from the administration of tacrolimus.

Figure 2 shows the extension on worm lifespan in Bu8 background caused by tacrolimus.

Figure 3 shows the delay in the time at which maximal lipid occurs in C. elegans caused by tacrolimus.

Figure 4 illustrates the model employed which demonstrated the reduction caused by tacrolimus on aging rats.

Figure 5 shows the reduction in body weights of aging rats caused by the administration of tacrolimus.

Figure 6 presents data showing the effect of tacrolimus on fat metabolites and various biochemical markers.

Figure 7 shows the effect on worms lifespan of tacrolimus and its close structural analogue ascomycin.

Figure 8 shows the effect on worms lifespan of tacrolimus and its close structural analogue dihydrotacrolimus.

Claims

~~1. A method of treatment of one or more conditions in a human in need thereof which comprises administering not more than once a day an effective amount of tacrolimus or a close structural analogue thereof which amount does not cause immunosuppression and which produces a whole blood trough level of tacrolimus or its close structural analogue of at least 0.05 ng/mL, wherein the one or more conditions is one or more of:~~

~~(i) adverse fat accumulation;~~
~~(ii) sarcopenia;~~
~~(iii) hyperglycaemia or type II diabetes;~~
~~(iv) high cholesterol;~~
~~(v) high triglycerides; or~~
~~(vi) metabolic syndrome.~~

21. Tacrolimus or a close structural analogue thereof for use in treating a condition at a dose which does not cause immunosuppression and which produces a whole blood trough level of tacrolimus or its close structural analogue of at least 0.05 ng/mL, wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

32. The use of tacrolimus or a close structural analogue thereof in the manufacture of a medicament for treating a condition which medicament does not cause immunosuppression and which produces a whole blood trough level of tacrolimus or its close structural analogue of at least 0.05 ng/mL, wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or

(vi) metabolic syndrome.

43. A compound or use ~~method~~ as claimed in ~~any of~~ claims 1 or 2 ~~to 3~~ where the trough whole blood level is at least 0.1 ng/mL~~.~~, and/or

~~5. A method as claimed in any of claims 1 to 3 wherein the trough whole blood level in at least 0.2 ng/mL.~~

~~6. A method as claimed in any of claims 1 to 5~~ wherein the trough whole blood level is less than 1.2 ng/mL.

~~7. A method as claimed in any of claims 1 to 6 wherein the trough whole blood level is less than 1.1 ng/mL.~~

84. A compound or use ~~method~~ as claimed in any of claims 1 to ~~7~~ 3 which employs tacrolimus.

~~9. A method of treatment of one or more conditions in a human in need thereof by administering not more than once a day a dose of tacrolimus or a close structural analogue wherein the dose is from 0.007 mg/kg to 0.03 mg/kg and the one or more conditions is one of more of:~~

~~(i) adverse fat accumulation;~~
~~(ii) sarcopenia;~~
~~(iii) hyperglycaemia or type II diabetes;~~
~~(iv) high cholesterol;~~
~~(v) high triglycerides; or~~
~~(vi) metabolic syndrome.~~

105. Tacrolimus or a close structural analogue thereof for use in treating one or more conditions where tacrolimus or its close structural analogue is administered not more than once a day at a dose of 0.007 mg/kg to 0.03 mg/kg and wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;

(v) high triglycerides; or

(vi) metabolic syndrome.

~~11~~6. The use of tacrolimus of a close structural analogue thereof for the manufacture of a medicament for the treatment of one or more conditions by administration not more than once a day wherein the medicament comprises 0.007 mg/kg to 0.03 mg/kg and where the one or more conditions is one or more of:

(i) adverse fat accumulation;

(ii) sarcopenia;

(iii) hyperglycaemia or type II diabetes;

(iv) high cholesterol;

(v) high triglycerides; or

(vi) metabolic syndrome.

~~12~~7. A compound ~~for~~ or use as claimed in ~~any of~~ claim~~s~~ 5 or 6 ~~8 to 11~~ which employs not more than 0.1 mg/kg, 0.085 mg/kg or 0.007 mg/kg~~.~~, and/or

~~13. A compound for use as claimed in any of claims 9 to 12~~ which employs more than 0.0014 mg/kg or more than 0.002 mg/kg.

~~14~~8. A compound ~~for~~ or use as claimed in any of claims ~~9~~ 5 to ~~13~~ 7 which employs 0.0014 mg/kg to 0.0085 mg/kg, for example 0.002 mg/kg to 0.007 mg/kg.

~~15~~9. A compound ~~for~~ or use as claimed in any of claims ~~9~~ 5 to ~~14~~ 8 which is tacrolimus.

~~16. A method of treatment of one or more conditions in a human in need thereof which comprises administration not more than once a day of an effective amount of tacrolimus or a close structural analogue sufficient to effect epigenetic modification which leads to a reduction in oxidative stress wherein the one or more conditions is one or more of:~~

~~(i) adverse fat accumulation;~~

~~(ii) sarcopenia;~~

~~(iii) hyperglycaemia or type II diabetes;~~

~~(iv) high cholesterol;~~

~~(v) high triglycerides; or~~

~~(vi) metabolic syndrome.~~

~~17~~10. Tacrolimus or a close structural analogue for use in treating one or more conditions by administration once a day of an amount which effects genetic modification which leads to a reduction in oxidative stress wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

~~18~~11. The use of tacrolimus or a close structural analogue in the manufacture of a medicament for the treatment of one or more conditions by administration not more than once a day which medicament contains an amount of tacrolimus or a close structural analogue thereof which effects epigenetic modification which leads to a reduction in oxidative stress and wherein the one or more conditions is one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

~~19~~12. A ~~method,~~ compound for use or use of a compound as claimed in ~~any of~~ claim~~s~~ 10 or 11 ~~16 to 18~~ which employs tacrolimus.

~~20~~13. A unit dose pharmaceutical composition which comprises 0.05 mg to 0.8 mg of tacrolimus or a close structural analogue thereof for use in the treatment of one or more of:

(i) adverse fat accumulation;
(ii) sarcopenia;
(iii) hyperglycaemia or type II diabetes;
(iv) high cholesterol;
(v) high triglycerides; or
(vi) metabolic syndrome.

~~21~~14. A unit dose pharmaceutical composition as claimed in claim ~~20~~ 13 which contains not more than 0.75 mg, 0.6 mg or 0.5 mg~~.~~, and/or

~~22. A unit dose pharmaceutical composition as claimed in either of claims 20 or 21~~ which contains not less than 0.05 mg, 0.1 mg or 0.15 mg.

~~23~~15. A unit dose pharmaceutical composition as claimed in ~~any of~~ claim~~s~~ 13 or 14 ~~20 to 22~~ which contains 0.1 mg to 0.6 mg.

~~24~~16. A unit dose pharmaceutical composition as claimed in any of claims ~~20~~ 13 to ~~23~~ 15 which contains tacrolimus.

~~25~~17. A ~~method,~~ compound for use, use of a compound or composition for use as claimed in any of claims 1 to ~~24~~ 16 in respect of adverse fat accumulation.

~~26. A method, composition for use, use of a compound or composition for use as claimed in any of claims 1 to 24 in respect of hyperglycaemia or type II diabetes.~~

~~27. A method, composition for use, use of a compound or composition for use as claimed in any of claims 1 to 24 in respect of high cholesterol.~~

~~28. A method, compound for use, use of a compound or composition for use as claimed in any of claims 1 to 24 in respect of high triglycerides.~~

~~29. A method, compound for use, use of a compound or composition for use as claimed in any of claims 1 to 24 in respect of metabolic syndrome.~~

~~30. A method, compound for use, use of a compound or composition for use as claimed in any of claims 1 to 24 in respect of sarcopenia.~~

~~31~~18. A ~~method,~~ composition for use, use of a compound or composition for use as claimed in any of claims 1 to ~~24~~ 17 in respect of 2, 3, 4, 5 or 6 of the conditions.

~~32~~19. A ~~method,~~ compound for use, use of a compound or composition for use as claimed in any of claims 1 to ~~31~~ 18 employed in respect of patient of over 40 years, over 50 years, over 60 years or over 70 years.

~~33~~20. ~~A method,~~ compound for use, use of a compound, composition for use as claimed in any of claims 1 to ~~32~~ 19 for use for a patient of body mass index greater than 40.

~~34~~21. ~~A method,~~ compound for use, use of a compound, composition for use as claimed in any of claims 1 to ~~32~~ 19 for use for a patient of body mass index of 25 to 40.

~~35~~22. A compound for use, use of a compound, composition for use ~~method~~ as claimed in any preceding claim in relation to ~~methods~~ uses that ~~is~~ are for cosmetic purposes.

~~36~~23. A ~~method,~~ compound for use, use of a compound or composition for use as claimed in any of claims 1 to ~~34~~ 21 for prophylactic use.

~~37~~24. A ~~method,~~ compound for use, use of a compound or composition for use as claimed in any of claims 1 to ~~34~~ 21 for therapeutic use.

~~38~~25. A ~~method,~~ compound for use, use of a compound or composition for use as claimed in any of claims 1 to ~~37~~ 24 for the reduction of fat accumulation followed by maintenance of the fat accumulation.

~~39~~26. A ~~method,~~ compound for use, use of a compound or composition for use as claimed in any of claims 1 to ~~38~~ 25 wherein the individual with adverse fat accumulation is aged between 30 to 50 years~~.~~, and/or

~~40. A method, compound for use, use of a compound or composition for use as claimed in any of claims 1 to 38~~ wherein the individual with adverse fat accumulation has a BMI of 25 to 35.

~~41~~27. A compound for use, use of a compound, composition for use ~~method~~ as claimed in any of claims 1 to ~~38~~ 25 wherein the dose of tacrolimus is 0.1 mg to 0.6 mg per day, for example 0.2 mg to 0.45 mg such as 0.3 mg per day.

~~42. A method of reducing serum triglyceride and/or cholesterol which comprises administering 0.05 mg to 0.65 mg of tacrolimus per day, for example 0.1 mg to 0.6 mg, such as 0.2 to 0.45 mg, for example 0.3 mg per day.~~

~~43. A method as claimed in claim 42 wherein administration is oral administration and/or administration once a day.~~

~~44. A method as claimed in either of claims 42 or 43 performed together with a method as claimed in any of claims 1 to 37.~~

4528. A unit dose pharmaceutical composition for use as claimed in any of claims ~~20~~ 13 to ~~24~~ 16 for oral administration once per day.

4629. A unit dose as claimed in claim ~~45~~ 28 which is a tablet or capsule.

4730. A unit dose as claimed in either of claims ~~45~~ 28 or ~~46~~ 29 which comprises 0.3 mg tacrolimus~~.~~,

~~48. A unit dose as claimed in either of claims 45 or 46 which comprises~~ 0.5 mg tacrolimus~~.~~, or

~~49. A unit dose as claimed in either of claims 45 or 46 which comprises~~ 0.6 mg tacrolimus.

5031. A unit dose as claimed in any of claims ~~45~~ 28 to ~~49~~ 30 for the treatment of adverse fat accumulation~~.~~, and/or

~~51. A unit dose as claimed in any of claims 45 to 49~~ for the prevention of age related fat accumulation.