

CLAIMS

1. A rodent, comprising a humanization of an endogenous rodent *Dpp4* gene, wherein the humanization comprises a replacement at the endogenous rodent *Dpp4* locus of a rodent gene encoding an exon of an *Dpp4* gene with a nucleic acid sequence encoding at least one exon of a human *DPP4* gene to form a modified *DPP4* gene, wherein expression of the modified *DPP4* gene is under control of rodent regulatory elements at the endogenous rodent *Dpp4* locus.
2. The rodent of claim 1, wherein the rodent is a mouse or a rat.
3. The rodent of claim 1, wherein the human *DPP4* gene encoding a human or humanized DPP4 protein comprises exon 2 through exon 26 of the human *DPP4* gene.
4. The rodent of claim 3, wherein the humanized DPP4 protein comprises the extracellular domain of the human DPP4 protein.
5. The rodent of claim 4, wherein the humanized DPP4 protein comprises the transmembrane domain and cytoplasmic domain of the mouse *Dpp4* protein.
6. The rodent of claim 1, wherein the rodent is a mouse that is incapable of expressing a mouse *Dpp4* protein.
7. The rodent of claim 1, wherein the rodent is a mouse, and wherein a contiguous genomic fragment of mouse *Dpp4* sequence encoding exon 2 through exon 26 of mouse *Dpp4* is replaced with a contiguous genomic fragment of human *DPP4* sequence encoding exon 2 through exon 26 of human *DPP4*.
8. The rodent of claim 1, wherein the rodent is a mouse that expresses human or humanized DPP4 protein on the surface of T cells, wherein the amount of T cells present

in the blood is at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% or 200% of the amount of T cells present in the blood of an age-matched mouse that expresses functional endogenous mouse Dpp4 protein, but does not comprise said replacement.

9. The rodent of claim 1, wherein the rodent is a mouse that expresses human or humanized DPP4 protein on the surface of T cells, wherein the amount of T cells present in the blood is between about 20% and about 200%, between about 40% and about 160%, or between about 80% and about 120% of the amount of T cells present in the blood of an age-matched mouse that expresses functional endogenous Dpp4 protein, but does not comprise said replacement.

10. The rodent of claim 1, wherein the rodent is a mouse that expresses human or humanized DPP4 protein on the surface of T cells in a level that is at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% or 200% of the level of mouse Dpp4 protein present on the surface of T cells of an age-matched mouse that expresses functional endogenous mouse Dpp4 protein, but does not comprise said replacement.

11. The rodent of claim 1, wherein the rodent is a mouse that expresses human or humanized DPP4 protein on the surface of T cells in a level that is between about 20% and about 200%, between about 40% and about 160%, or between about 80% and about 120% of the level of mouse Dpp4 protein present on the surface of T cells of an age-matched mouse that expresses functional endogenous Dpp4 protein, but does not comprise said replacement.

12. The rodent of claim 1, wherein the rodent is a mouse that expresses human or humanized DPP4 protein on the surface of cells in one or more tissues selected from the group consisting of placenta, kidney, lung, liver, skeletal muscle, heart, brain and pancreas, in a level that is at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% or 200% of the level of mouse Dpp4 protein present on the surface of the one or more tissues of an age-

matched mouse that expresses functional endogenous mouse *Dpp4* protein, but does not comprise said replacement.

13. The rodent of claim 1, wherein the rodent is a mouse that expresses human or humanized DPP4 protein on the surface of cells in one or more tissues selected from the group consisting of placenta, kidney, lung, liver, skeletal muscle, heart, brain and pancreas, at a level that is between about 20% and about 200%, between about 40% and about 160%, or between about 80% and about 120% of the level of mouse *Dpp4* protein present on the surface of the one or more tissues of an age-matched mouse that expresses functional endogenous *Dpp4* protein, but does not comprise said replacement.

14. The rodent of any one of claims 1-13, wherein the humanization of the endogenous rodent *Dpp4* gene is heterozygous.

15. The rodent of any one of claims 1-13, wherein the humanization of the endogenous rodent *Dpp4* gene is homozygous.

16. A method for making a humanized rodent, comprising replacing a rodent *Dpp4* gene sequence encoding rodent *Dpp4* protein with a human *DPP4* gene sequence comprising one or more exons of the human *DPP4* gene sequence encoding human or humanized DPP4 protein, wherein the replacement is at an endogenous rodent *Dpp4* locus and the human *DPP4* gene sequence comprising one or more exons of the human *DPP4* gene sequence encoding human or humanized DPP4 protein is operably linked to rodent regulatory elements or sequences at the endogenous rodent *Dpp4* locus.

17. The method of claim 16, wherein the rodent is a mouse or a rat.

18. The method of claim 16, wherein the rodent regulatory elements or sequences are from a mouse or a rat.

19. The method of claim 16, wherein the rodent regulatory elements or sequences are endogenous rodent regulatory elements or sequences at the rodent *Dpp4* locus.
20. The method of claim 16, wherein the human *DPP4* gene sequence replacing the rodent *Dpp4* gene sequence comprises at least one exon of the human *DPP4* gene sequence.
21. The method of claim 20, wherein the human *DPP4* gene sequence replacing the rodent *Dpp4* gene sequence comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, 24, or 25 exons of the human *DPP4* gene sequence.
22. The method of claim 21, wherein the human *DPP4* gene sequence replacing the rodent *Dpp4* gene sequence comprises all 26 exons of the human *DPP4* gene sequence.
23. The method of claim 16, wherein the human *DPP4* gene sequence replacing the rodent *Dpp4* gene sequence comprises at least one exon of the human *DPP4* gene sequence encoding the extracellular domain of the human DPP4 protein.
24. The method of claim 23, wherein the human *DPP4* gene sequence replacing the rodent *Dpp4* gene sequence comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, or 23 exons of the human *DPP4* gene sequence encoding the extracellular domain of the human DPP4 protein.
25. The method of claim 24, wherein the human *DPP4* gene sequence replacing the rodent *Dpp4* gene sequence comprises all 24 exons of the human *DPP4* gene sequence encoding the extracellular domain of the human DPP4 protein.
26. The method of claim 17, wherein the replacement is at an endogenous rodent *Dpp4* locus and the human *DPP4* gene sequence comprising one or more exons of the human *DPP4* gene sequence encoding human or humanized DPP4 protein is operably

linked endogenous rodent regulatory elements or sequences at the endogenous rodent *Dpp4* locus.

27. The method of any one of claims 16-26, wherein the rodent is heterozygous for the human *DPP4* gene sequence comprising one or more exons of the human *DPP4* gene sequence encoding the human or humanized DPP4 protein.

28. The method of any one of claims 16-26, wherein the rodent is homozygous for the human *DPP4* gene sequence comprising one or more exons of the human *DPP4* gene sequence encoding the human or humanized DPP4 protein.

29. A method for making a humanized *DPP4* mouse, comprising replacing a mouse *Dpp4* gene sequence encoding mouse Dpp4 protein with a human *DPP4* gene encoding human or humanized DPP4 protein.

30. The method of claim 29, wherein the replacement is at an endogenous mouse *Dpp4* locus, and the human *DPP4* gene encoding human or humanized DPP4 protein is operably linked to mouse regulatory sequences.

31. The method of claim 29, wherein the replacement is at an endogenous mouse *Dpp4* locus, and the human *DPP4* gene encoding human or humanized DPP4 protein is operably linked to endogenous mouse regulatory sequences.

32. The method of any one of claims 29-31, wherein the mouse is heterozygous for the human *DPP4* gene encoding the human or humanized DPP4 protein.

33. The method of any one of claims 29-31, wherein the mouse is homozygous for the human *DPP4* gene encoding the human or humanized DPP4 protein.

34. A rodent comprising a nucleic acid sequence comprising a human *DPP4* gene or fragment thereof, wherein the human *DPP4* gene or fragment thereof comprises at least

one exon of the human *DPP4* gene, and wherein the human *DPP4* gene or fragment thereof encodes a human or humanized DPP4 protein.

35. The rodent of claim 34, wherein the human *DPP4* gene or fragment thereof comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, 24, or 25 exons of the human *DPP4* gene.

36. The rodent of claim 34, wherein the human *DPP4* gene or fragment thereof comprises all 26 exons of the human *DPP4* gene.

37. The rodent of claim 34, wherein the nucleic acid sequence further comprises a 5' flanking region of the human *DPP4* gene.

38. The rodent of claim 37, wherein the human *DPP4* gene or fragment thereof is operably linked to the 5' flanking region of the human *DPP4* gene.

39. The rodent of claim 38, wherein the 5' flanking region of the human *DPP4* gene comprises at least 10 kb in length.

40. The rodent of claim 39, wherein the 5' flanking region of the human *DPP4* gene comprises at least 40 kb in length.

41. The rodent of claim 38, wherein expression of the human *DPP4* gene or fragment thereof is under control of the 5' flanking region of the human *DPP4* gene.

42. The rodent of claim 34, wherein the human or humanized DPP4 protein comprises the amino acid sequence of SEQ ID NO: 24 or a fragment thereof.

43. The rodent of claim 38, wherein the rodent expresses the human or humanized DPP4 protein on the surface of T cells in a level that is at least about 20% of the level of

rodent Dpp4 protein present on the surface of T cells of an age-matched rodent that expresses functional endogenous rodent Dpp4 protein but that does not comprise the human *DPP4* gene or fragment thereof.

44. The rodent of claim 38, wherein the rodent expresses the human or humanized DPP4 protein on the surface of cells in one or more tissues selected from the group consisting of placenta, kidney, lung, liver, skeletal muscle, heart, brain, and pancreas, in a level that is at least about 20% of the level of rodent Dpp4 protein present on the surface of one or more tissues of an age-matched rodent that expresses functional endogenous rodent Dpp4 protein but that does not comprise the human *DPP4* gene or fragment thereof.

45. The rodent of claim 34, wherein the rodent expresses functional endogenous rodent Dpp4 protein.

46. The rodent of claim 34, wherein the rodent is a mouse or a rat.

47. The rodent of any one of claims 34-46, wherein the rodent is heterozygous for the human *DPP4* gene or fragment thereof.

48. The rodent of any one of claims 34-46, wherein the rodent is homozygous for the human *DPP4* gene or fragment thereof.

49. A method for making a humanized transgenic rodent, comprising integrating a nucleic acid sequence comprising one or more exons of a human *DPP4* gene sequence into a chromosome of a rodent, wherein the one or more exons of the human *DPP4* gene sequence encodes a human or humanized DPP4 protein.

50. The method of claim 49, wherein the human *DPP4* gene or fragment thereof comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, 24, or 25 exons of the human *DPP4* gene.

51. The method of claim 49, wherein the human *DPP4* gene or fragment thereof comprises all 26 exons of the human *DPP4* gene.
52. The method of claim 49, wherein the nucleic acid sequence further comprises a 5' flanking region of the human *DPP4* gene.
53. The method of claim 52, wherein the human *DPP4* gene sequence is operably linked to the 5' flanking region of the human *DPP4* gene.
54. The method of claim 49, wherein the human or humanized DPP4 protein comprises the amino acid sequence of SEQ ID NO: 24 or a fragment thereof.
55. The method of claim 49, wherein the rodent is a mouse or a rat.
56. The method of any one of claims 49-55, wherein the rodent is heterozygous for the for the nucleic acid sequence comprising one or more exons of a human *DPP4* gene sequence.
57. The method of any one of claims 49-55, wherein the rodent is homozygous for the for the nucleic acid sequence comprising one or more exons of a human *DPP4* gene sequence.
58. A method for determining the *in vivo* therapeutic efficacy of a human-specific DPP4 antagonist in the rodent of any one of claims 1-15 or 34-48, the method comprising:
- (a) administering to the rodent a DPP4 antagonist, wherein the rodent is infected with Middle East respiratory syndrome coronavirus (MERS-CoV); and

(b) determining if the DPP4 antagonist treats or prevents one or more symptoms of MERS-CoV infection compared to control rodents infected with MERS-CoV who have not been administered the DPP4 antagonist.

59. The method of claim 58, wherein the DPP4 antagonist is selected from the group consisting of small molecules, peptides and antibodies.

60. The method of claim 58 or 59, wherein the DPP4 antagonist is an antibody to a MERS-CoV protein.

61. The method of claim 60, wherein the MERS-CoV protein is MERS-CoV spike protein.

62. The method of any one of claims 58-61, wherein the rodent is infected with one or more strains of MERS-CoV selected from the group consisting of Al-Hasa_1, Al-Hasa_2, Al-Hasa_3, Al-Hasa_4, Al-Hasa_12, Al-Hasa_15, Al-Hasa_16, Al-Hasa_17, Al-Hasa_18, Al-Hasa_19, Al-Hasa_21, Al-Hasa_25, Buraidah_1, EMC/2012, FRA/UAE, Hafr-Al-Batin_1, Hafr-Al-Batin_2, Hafr-Al-Batin_6, Jeddah_1, Jordan-N3/2012, Munich, Riyadh_3, Riyadh_4, Riyadh_5, Riyadh_14, Taif_1, Wadi-Ad-Dawasir_1, Riyadh_9, KFU-HKU 1, KFU-HKU 13, Qatar3, Qatar4, England 1, England-Qatar/2012, Bisha_1, Riyadh_1, and Riyadh_2.

63. The method of any one of claims 58-62, wherein the antagonist is administered before MERS-CoV infection.

64. The method of any one of claims 58-62, wherein the antagonist is administered after MERS-CoV infection.

65. The method of any one of claims 58-62, wherein the antagonist is administered simultaneously with MERS-CoV infection.

66. The method of any one of claims 58-65, wherein the symptom of MERS-CoV infection is viral titer or RNA level.
67. The method of claim 66, wherein viral titer or RNA level is assessed by one or more methods selected from the group consisting of qPCR, Northern Blot, plaque assay, and *in situ* hybridization.
68. The method of any one of claims 58-65, wherein the symptom of MERS-CoV infection is lung inflammation.
69. The method of claim 68, wherein lung inflammation is assessed histochemically.
70. The method of any one of claims 58-65, wherein the symptom of MERS-CoV infection is weight loss.

CLAIMS

1. A rodent, comprising a humanization of an endogenous rodent Dpp4 gene, wherein the humanization comprises a replacement at the endogenous rodent Dpp4 locus of a rodent gene encoding an exon of an Dpp4 gene with a nucleic acid sequence encoding exon 2 through exon 26 of a human DPP4 gene to form a modified DPP4 gene, wherein expression of the modified DPP4 gene is under control of rodent regulatory elements at the endogenous rodent Dpp4 locus, wherein the rodent is a mouse or a rat, and wherein the rodent exhibits one or more symptoms when infected with Middle East respiratory syndrome coronavirus (MERS-CoV).
2. The rodent of claim 1, wherein the rodent is a mouse that is incapable of expressing a mouse Dpp4 protein.
3. The rodent of claims 1 or 2, wherein the humanization of the endogenous rodent Dpp4 gene is heterozygous.
4. The rodent of claims 1 or 2, wherein the humanization of the endogenous rodent Dpp4 gene is homozygous.
5. A method for making a humanized rodent, comprising replacing a rodent Dpp4 gene sequence encoding rodent Dpp4 protein with a human DPP4 gene sequence comprising exon 2 through exon 26 of the human DPP4 gene sequence encoding human or humanized DPP4 protein, wherein the replacement is at an endogenous rodent Dpp4 locus and the human DPP4 gene sequence comprising exon 2 through exon 26 of the human DPP4 gene sequence encoding human or humanized DPP4 protein is operably linked to rodent regulatory elements or sequences at the endogenous rodent Dpp4 locus, wherein the rodent is a mouse or a rat, and wherein the rodent exhibits one or more symptoms when infected with Middle East respiratory syndrome coronavirus (MERS-CoV).
6. The method of claim 5, wherein the rodent regulatory elements or sequences are from a mouse or a rat.

7. The method of claims 5 or 6, wherein the rodent regulatory elements or sequences are endogenous rodent regulatory elements or sequences at the rodent Dpp4 locus.
8. The method of any one of the preceding claims, wherein the human DPP4 gene sequence replacing the rodent Dpp4 gene sequence comprises all 26 exons of the human DPP4 gene sequence.
9. The method of any one of the preceding claims, wherein the rodent is heterozygous for the human DPP4 gene sequence comprising exon 2 through exon 26 of the human DPP4 gene sequence encoding the human or humanized DPP4 protein.
10. The method of any one of the preceding claims, wherein the rodent is homozygous for the human DPP4 gene sequence comprising exon 2 through exon 26 of the human DPP4 gene sequence encoding the human or humanized DPP4 protein.
11. A method for determining the in vivo therapeutic efficacy of a human-specific DPP4 antagonist in the rodent of claim 1, the method comprising:
 - (a) administering to the rodent a DPP4 antagonist, wherein the rodent is infected with Middle East respiratory syndrome coronavirus (MERS-CoV); and
 - (b) determining if the DPP4 antagonist treats or prevents one or more symptoms of MERS-CoV infection compared to control rodents infected with MERS-CoV who have not been administered the DPP4 antagonist.
12. The method of claim 11, wherein the DPP4 antagonist is selected from the group consisting of small molecules, peptides and antibodies.
13. The method of claims 11 or 12, wherein the DPP4 antagonist is an antibody to a MERS-CoV protein.
14. The method of claim 13, wherein the MERS-CoV protein is MERS-CoV spike protein.
15. The method of any one of the preceding claims, wherein the antagonist is administered before MERS-CoV infection.

16. The method of any one of the preceding claims, wherein the antagonist is administered after MERS-CoV infection.
17. The method of any one of the preceding claims, wherein the antagonist is administered simultaneously with MERS-CoV infection.
18. The method of any one of the preceding claims, wherein the symptom of MERS-CoV infection is viral titer or RNA level.
19. The method of claim 18, wherein viral titer or RNA level is assessed by one or more methods selected from the group consisting of qPCR, Northern Blot, plaque assay, and in situ hybridization.
20. The method of claim any one of the preceding claims, wherein the symptom of MERS-CoV infection is lung inflammation.
21. The method of claim 20, wherein lung inflammation is assessed histochemically.
22. The method of claim any one of the preceding claims, wherein the symptom of MERS-CoV infection is weight loss.