

CLAIMS

1. A rodent, comprising a replacement at an endogenous rodent C3 locus of a rodent gene sequence encoding an exon of a C3 gene with a nucleic acid sequence encoding at least one exon of a human C3 gene to form a modified C3 gene, wherein expression of the modified C3 gene is under control of rodent regulatory elements at the endogenous rodent C3 locus.
2. The rodent of claim 1, wherein the rodent is a mouse or a rat
3. The rodent of claim 1 or claim 2, wherein the human C3 gene encoding human C3 protein comprises exon 1 through exon 41 of the human C3 gene.
4. The rodent of any one of claims 1-3, wherein the human C3 gene encoding human C3 protein comprises exon 2 through exon 41 of the human C3 gene.
5. The rodent of any one of claims 1-4, wherein the rodent is a mouse that is incapable of expressing a mouse C3 protein.
6. The rodent of any one of claims 1-5, wherein the rodent is a mouse that expresses a mouse C5 protein encoded by an endogenous mouse C5 gene.
7. The rodent of claim 5, wherein the mouse expresses a human or humanized C5 protein.
8. The rodent of claim 7, wherein the mouse comprises a replacement at an endogenous mouse C5 locus of a mouse gene encoding C5 protein with a human C5 gene encoding human C5 protein.
9. The rodent of claim 7 or claim 8, wherein expression of the human C5 gene is under control of mouse regulatory elements at the endogenous mouse C5 locus.

10. The rodent of any one of claims 1-9, wherein the rodent is a mouse that expresses human C3 protein in serum at a concentration of at least about 10%, 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 C3 protein present in the serum of an age-matched mouse that expresses functional endogenous mouse C3 protein, but does not comprise said replacement.
11. The rodent of any one of claims 1-10, wherein the rodent is a mouse that expresses human C3 protein in serum at a concentration of between about 10% and about 200%, between about 20% and about 150%, or between about 30% and about 100% of the level of mouse C3 protein present in the serum of an age-matched mouse that expresses functional endogenous mouse C3 protein, but does not comprise said replacement.
12. The rodent of any one of claims 1-11, wherein the rodent is a mouse that expresses human C3 protein in serum at a concentration of between about 100 µg/ml and about 1500 µg/ml, between about 200 µg/ml and about 1250 µg/ml, or between about 300 µg/ml and about 1000 µg/ml.
13. The rodent of any one of claims 1-12, wherein the rodent is a mouse that expresses human C3 protein in serum at a concentration of at least about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1250 or 1500 µg/ml.
14. A method for making a humanized rodent, comprising replacing a rodent C3 gene sequence encoding rodent C3 protein with a human C3 gene sequence comprising one or more exons of the human C3 gene sequence encoding human or humanized C3 protein, wherein the replacement is at an endogenous rodent C3 locus and the human C3 gene sequence comprising one or more exons of the human C3 gene sequence encoding human or humanized C3 protein is operably linked to rodent regulatory elements or sequences at the endogenous rodent C3 locus.
15. The method of claim 14, wherein the rodent is a mouse or a rat.
16. The method of claim 14 or 15, wherein the rodent regulatory elements or sequences

are from a mouse or a rat.

17. The method of any one of claims 14-16, wherein the rodent regulatory elements or sequences are endogenous rodent regulatory elements or sequences at the rodent C3 locus.

18. The method of any one of claims 14-17, wherein the human C3 gene sequence replacing the rodent C3 gene sequence comprises at least one exon of the human C3 gene sequence.

19. The method of claim 18, wherein the human C3 gene sequence replacing the rodent C3 gene sequence comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 exons of the human C3 gene sequence.

20. The method of claim 19, wherein the human C3 gene sequence replacing the rodent C3 gene sequence comprises all 41 exons of the human C3 gene sequence.

21. The method of any one of claims 14-20, wherein the replacement is at an endogenous rodent C3 locus and the human C3 gene sequence comprising one or more exons of the human C3 gene sequence encoding human or humanized C3 protein is operably linked endogenous rodent regulatory elements or sequences at the endogenous rodent C3 locus.

22. A method for making a humanized mouse, comprising replacing a mouse C3 gene sequence encoding mouse C3 protein with a human C3 gene encoding human C3 protein.

23. The method of claim 22, wherein the replacement is at an endogenous mouse C3 locus, and the human C3 gene encoding human C3 protein is operably linked to endogenous mouse regulatory sequences at the endogenous mouse C3 locus.

24. A rodent, comprising a humanized C5 gene comprising a replacement at an

endogenous rodent C5 locus of a rodent gene encoding C5 protein with a human C5 gene encoding human or humanized C5 protein, wherein expression of the human C5 gene encoding human or humanized C5 protein is under control of rodent regulatory elements or sequences at the endogenous rodent C5 locus, and wherein the rodent further comprises a replacement at an endogenous rodent C3 locus of a rodent gene encoding C3 protein with a human C3 gene encoding human or humanized C3 protein, wherein expression of the human C3 gene encoding human or humanized C3 protein is under control of rodent regulatory elements or sequences at the endogenous rodent C3 locus.

25. The rodent of claim 24, wherein the rodent is a mouse or a rat.

26. The rodent of claim 25, wherein the rodent is a mouse that is incapable of expressing a mouse C5 protein and incapable of expressing a mouse C3 protein.

27. The rodent of claim 24, wherein the rodent regulatory elements or sequences at the endogenous rodent C5 locus and/or endogenous rodent C3 locus are from a mouse or a rat.

28. The rodent of claim 24, wherein the rodent regulatory elements or sequences are endogenous rodent regulatory elements or sequences at the rodent C5 locus and/or rodent C3 locus.

29. A rodent, comprising a replacement at an endogenous rodent C5 locus of a rodent gene sequence encoding an exon of a C5 gene with a nucleic acid sequence encoding at least one exon of a human C5 gene to form a modified C5 gene, wherein expression of the modified C5 gene is under control of rodent regulatory elements at the endogenous rodent C5 locus, wherein the human C5 gene encoding human C5 protein comprises exon 2 through exon 41 of the human C5 gene.

30. The rodent of claim 29, wherein the rodent is a mouse or a rat.

31. The rodent of claim 29 or claim 30, wherein the rodent is a mouse that is incapable of expressing a mouse C5 protein.

32. The rodent of any one of claims 29-31, wherein the rodent is a mouse that expresses a mouse C3 protein encoded by an endogenous mouse C3 gene.
33. The rodent of any one of claims 29-32, wherein the rodent is a mouse that expresses a human or humanized C3 protein.
34. The rodent of claim 33, wherein the mouse comprises a replacement at an endogenous mouse C3 locus of a mouse gene encoding C3 protein with a human C3 gene encoding a human C3 protein.
35. The rodent of claim 33 or claim 34, wherein expression of the human C3 gene is under control of mouse regulatory elements at the endogenous mouse C3 locus.
36. The rodent of any one of claims 29-35, wherein the rodent is a mouse that expresses human C5 protein in serum at a concentration of at least about 10%, 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 C5 protein present in the serum of an age-matched mouse that expresses functional endogenous mouse C5 protein, but does not comprise said replacement.
37. The rodent of any one of claims 29-36, wherein the rodent is a mouse that expresses human C5 protein in serum at a concentration of between about 10% and about 200%, between about 20% and about 150%, or between about 30% and about 100% of the level of mouse C5 protein present in the serum of an age-matched mouse that expresses functional endogenous C5 protein, but does not comprise said replacement.
38. The rodent of any one of claims 29-37, wherein the rodent is a mouse that expresses human C5 protein in serum at a concentration of between about 10 µg/ml and about 150 µg/ml, between about 10 µg/ml and about 125 µg/ml, or between about 15 µg/ml and about 100 µg/ml.

39. The rodent of any one of claims 29-38, wherein the rodent is a mouse that expresses human C5 protein in serum at a concentration of at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125 or 150 $\mu\text{g/ml}$.

40. A method for making a humanized rodent, comprising replacing a rodent C5 gene sequence encoding rodent C5 protein with a human C5 gene sequence comprising one or more exons of the human C5 gene sequence encoding human or humanized C5 protein, wherein the replacement is at an endogenous rodent C5 locus and the human C5 gene sequence comprising one or more exons of the human C5 gene sequence encoding human or humanized C5 protein is operably linked to rodent regulatory elements or sequences at the endogenous rodent C5 locus, wherein the rodent regulatory elements or sequences are from a mouse or a rat.

41. The method of claim 40, wherein the rodent is a mouse or a rat.

43. The method of claim 40 or claim 41, wherein the rodent regulatory elements or sequences are endogenous rodent regulatory elements or sequences at the rodent C5 locus.

43. The method of any one of claims 40-42, wherein the human C5 gene sequence replacing the rodent C5 gene sequence comprises at least one exon of the human C5 gene sequence.

44. The method of claim 43, wherein the human C5 gene sequence replacing the rodent C5 gene sequence comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 exons of the human C5 gene sequence.

45. The method of claim 43 or claim 44, wherein the human C5 gene sequence replacing the rodent C5 gene sequence comprises all 41 exons of the human C5 gene sequence.

46. The method of any one of claims 40-45, wherein the replacement is at an endogenous rodent C5 locus and the human C5 gene sequence comprising one or more exons of the human C5 gene sequence encoding human or humanized C5 protein is operably linked endogenous rodent regulatory elements or sequences at the endogenous rodent C5 locus.
47. A method for making a humanized mouse, comprising replacing a mouse C5 gene sequence encoding mouse C5 protein with a human C5 gene encoding human C5 protein, wherein the replacement is at an endogenous mouse C5 locus, and the human C5 gene encoding human C5 protein is operably linked to endogenous mouse regulatory sequences at the endogenous mouse C5 locus.
48. A method for identifying a compound capable of modulating complement activation comprising:
- a. administering the compound to the rodent of any one of claims 1-12 or 24-39; and
 - b. assaying if complement activation in the rodent is modulated, thereby identifying a compound capable of modulating complement activation.
49. The method of claim 48, wherein the compound is a small molecule chemical compound, an antibody, a protein, an inhibitory nucleic acid, or any combination thereof.
50. The method of claim 48 or claim 49, wherein the compound modulates complement activation by increasing complement activity.
51. The method of claim 48 or claim 49, wherein the compound modulates complement activation by decreasing complement activity.
52. The method of any one of claims 48-51, wherein the serum of the rodent is assayed to determine if complement activation in the rodent is modulated.

53. The method of claim 52, wherein the assay is the CH₅₀ complement screening assay