

CLAIMS

1. A genetically modified murine animal comprising a replacement at an endogenous murine IL-6 locus of a murine gene encoding IL-6 with a human gene
5 encoding human IL-6, wherein the human gene encoding human IL-6 is under control of endogenous murine regulatory elements at the endogenous murine IL-6 locus, and wherein the murine animal is a rat.
2. The genetically modified murine animal of claim 1, wherein the human gene
10 encoding human IL-6 comprises exons 1 through 5 of the human IL-6 gene found in the CTD-2369M23 bacterial artificial chromosome.
3. The genetically modified murine animal of claim 1, wherein the murine animal expresses a humanized IL-6R α wherein the endogenous murine IL-6R α gene has been
15 replaced with a human sequence comprising a sequence that encodes an ectodomain of a human IL-6R α .
4. The genetically modified murine animal of claim 1, wherein the murine animal does not exhibit a feature selected from plasmocytosis, glomerulosclerosis,
20 glomerulonephritis, kidney failure, hypergammaglobulinemia, elevated megakaryocytes in spleen, elevated megakaryocytes in bone marrow, splenomegaly, lymph node enlargement, compacted abnormal plasma cells, and a combination thereof.
5. The genetically modified murine animal of claim 3, wherein the humanized IL-
25 6R α comprises murine transmembrane and intracellular domains.
6. A genetically modified murine animal, comprising a humanization of an endogenous murine IL-6R α gene, wherein the humanization comprises a replacement of murine IL-6R α ectodomain-encoding sequence with human IL-6R α ectodomain-
30 encoding sequence at the endogenous murine IL-6R α locus, wherein the humanized IL-

6R α gene is under control of endogenous murine regulatory elements, and wherein the murine animal is a rat.

7. The genetically modified murine animal of claim 6, further comprising a humanized IL-6 gene comprising a replacement at an endogenous murine IL-6 locus of a murine gene encoding IL-6 with a human gene encoding human IL-6.

8. A method for making a humanized murine animal, comprising replacing a murine gene sequence encoding murine IL-6 with a human gene encoding human IL-6 so that the human IL-6 gene is under control of endogenous murine regulatory elements, wherein the murine animal is a rat.

9. A method for making a humanized murine animal, comprising replacing all murine exons encoding ectodomain sequences of murine IL-6R α with a human genomic fragment encoding human IL-6R α ectodomain to form a humanized IL-6R α gene, wherein the humanized IL-6R α gene is under control of endogenous murine regulatory elements, and wherein the murine animal is a rat.

10. A genetically modified murine animal comprising a humanized IL-6R α gene comprising a replacement of murine ectodomain-encoding sequence with human ectodomain sequence, wherein the humanized IL-6R α gene comprises murine transmembrane and intracellular domain sequences, wherein the murine animal further comprises a gene encoding a human IL-6, wherein the genes encoding human IL-6 and humanized IL-6R α are under control of endogenous murine regulatory elements, and wherein the murine animal is a rat.

11. A murine embryonic stem (ES) cell, comprising a replacement of a murine gene encoding IL-6 at an endogenous murine IL-6 locus with a human gene encoding human IL-6, wherein the human gene encoding human IL-6 is under control of endogenous murine regulatory elements at the endogenous murine IL-6 locus, and wherein the murine ES cell is a mouse ES cell or a rat ES cell.

12. The murine ES cell of claim 11, wherein the murine ES cell is a mouse ES cell.
13. The murine ES cell of claim 11, wherein the murine ES cell is a rat ES cell.
14. The murine ES cell of claim 11, wherein the murine ES cell is heterozygous with respect to the replacement at the endogenous murine IL-6 locus.
- 5 15. The murine ES cell of claim 11, wherein the murine ES cell is homozygous with respect to the replacement at the endogenous murine IL-6 locus.
16. A murine embryo comprising the murine ES cell of claim 11.
17. A murine ES cell, comprising a replacement of a murine nucleic acid encoding a murine IL-6R α ectodomain at an endogenous murine IL-6R α locus with a human
10 nucleic acid encoding a human IL-6R α ectodomain to form a humanized IL-6R α gene, wherein the humanized IL-6R α gene is under control of endogenous murine regulatory elements at the endogenous murine IL-6R α locus, wherein the humanized IL-6R α gene encodes a humanized IL-6R α protein which comprises the human IL-6R α ectodomain and murine IL-6R α transmembrane and cytoplasmic domains; and wherein the murine
15 ES cell is a mouse ES cell or a rat ES cell.
18. The murine ES cell of claim 17, wherein the murine ES cell is a mouse ES cell.
19. The murine ES cell of claim 17, wherein the murine ES cell is a rat ES cell.
20. The murine ES cell of claim 17, wherein the murine ES cell is heterozygous with respect to the replacement at the endogenous murine IL-6R α locus.
- 20 21. The murine ES cell of claim 17, wherein the murine ES cell is homozygous with respect to the replacement at the endogenous murine IL-6R α locus.
22. A murine embryo comprising the murine ES cell of claim 17.
23. A murine ES cell, comprising

(i) a replacement of a murine gene encoding IL-6 at an endogenous murine IL-6 locus with a human gene encoding human IL-6, wherein the human gene encoding human IL-6 is under control of endogenous murine regulatory elements at the endogenous murine IL-6 locus; and

5 (ii) a replacement of a murine nucleic acid encoding a murine IL-6R α ectodomain at an endogenous murine IL-6R α locus with a human nucleic acid encoding a human IL-6R α ectodomain to form a humanized IL-6R α gene, wherein the humanized IL-6R α gene is under control of endogenous murine regulatory elements at the endogenous murine IL-6R α locus, wherein the humanized IL-
10 6R α gene encodes a humanized IL-6R α protein which comprises the human IL-6R α ectodomain and murine IL-6R α transmembrane and cytoplasmic domains; and

wherein the murine ES cell is a mouse ES cell or a rat ES cell.

24. The murine ES cell of claim 23, wherein the murine ES cell is a mouse ES cell.

15 25. The murine ES cell of claim 23, wherein the murine ES cell is a rat ES cell.

26. The murine ES cell of claim 23, wherein the murine ES cell is homozygous with respect to the replacement at the endogenous murine IL-6 locus, and with respect to the replacement at the endogenous murine IL-6R α locus.

27. A murine embryo comprising the murine ES cell of claim 23.