

We claim:

1. A genetically modified mouse comprising a replacement at an endogenous mouse IL-6 locus of a mouse gene encoding IL-6 with a human gene encoding human IL-6, wherein the human gene encoding human IL-6 is under control of endogenous mouse regulatory elements at the endogenous mouse IL-6 locus.
2. The genetically modified mouse of claim 1, wherein the human gene encoding human IL-6 is a human IL-6 gene of BAC ID CTD-2369M23.
3. The genetically modified mouse of claim 1, wherein the mouse expresses a mouse IL-6R α .
4. The genetically modified mouse of claim 1, wherein the mouse expresses a humanized IL-6R α .
5. The genetically modified mouse of claim 1, wherein the mouse expresses a humanized IL-6R α .
6. The genetically modified mouse of claim 1, wherein the mouse does not exhibit a feature selected from plasmocytosis, glomerulosclerosis, 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.
7. The genetically modified mouse of claim 4, wherein the humanized IL-6R α comprises a human ectodomain.
8. The genetically modified mouse of claim 7, wherein the humanized IL-6R α comprises a mouse transmembrane domain and a mouse cytoplasmic domain.
9. A genetically modified mouse, comprising a humanization of an endogenous mouse IL-6R α gene, wherein the humanization comprises a replacement of mouse IL-6R α ectodomain-encoding sequence with human IL-6R α ectodomain-encoding sequence at the endogenous mouse IL-6R α locus.

10. The genetically modified mouse of claim 9, wherein a contiguous mouse sequence comprising mouse exons 1 through 8 is replaced with a contiguous genomic fragment of human IL-6R α sequence encoding a human IL-6R α ectodomain.
11. The genetically modified mouse of claim 10, wherein the contiguous genomic fragment of human IL-6R α sequence encoding the ectodomain is from BAC CTD-2192J23.
12. The genetically modified mouse of claim 9, further comprising a humanized IL-6 gene.
13. The genetically modified mouse of claim 12, wherein the mouse comprises a replacement at an endogenous mouse IL-6 locus of a mouse IL-6 gene with a human IL-6 gene.
14. The genetically modified mouse of claim 12, wherein the humanized IL-6 gene is under control of endogenous mouse regulatory elements.
15. A method for making a humanized mouse, comprising replacing a mouse gene sequence encoding mouse IL-6 with a human gene encoding human IL-6.
16. The method of claim 15, wherein the replacement is at an endogenous mouse IL-6 locus, and the human gene encoding human IL-6 is operably linked to endogenous mouse regulatory sequences.
17. A method for making a humanized mouse, comprising replacing mouse exons encoding ectodomain sequences of mouse IL-6R α with a human genomic fragment encoding ectodomain sequences of human IL-6R α to form a humanized IL-6R α gene.
18. The method of claim 17, wherein the replacement is at an endogenous mouse IL-6R α locus, and the humanized IL-6R α gene is operably linked to endogenous mouse regulatory sequences.

19. A genetically modified mouse comprising a humanized IL-6R α gene comprising a replacement of mouse ectodomain-encoding sequence with human ectodomain sequence, wherein the humanized IL-6R α gene comprises a mouse transmembrane sequence and a mouse cytoplasmic sequence; wherein the mouse further comprises a gene encoding a human IL-6, wherein the gene encoding a human IL-6 is under control of endogenous mouse IL-6 regulatory elements.

20. The genetically modified mouse of claim 19, wherein the mouse is incapable of expressing a fully mouse IL-6R α and incapable of expressing a mouse IL-6.

CLAIMS

1. A genetically modified mouse comprising a replacement at an endogenous mouse IL-6 locus of a mouse gene encoding IL-6 with a human gene encoding human IL-6, wherein the human gene encoding human IL-6 is under control of endogenous mouse regulatory elements at the endogenous mouse IL-6 locus.
2. The genetically modified mouse of claim 1, wherein the human gene 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 mouse of claim 1, wherein the mouse expresses a mouse IL-6R α .
4. The genetically modified mouse of claim 1, wherein the mouse expresses a humanized IL-6R α wherein the endogenous mouse IL-6R α gene has been replaced with a human sequence comprising a sequence that encodes an ectodomain of a human IL-6R α .
5. The genetically modified mouse of claim 1, wherein the mouse does not exhibit a feature selected from plasmocytosis, glomerulosclerosis, 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.
6. The genetically modified mouse of claim 4, wherein the humanized IL-6R α comprises a human ectodomain.
7. The genetically modified mouse of claim 6, wherein the humanized IL-6R α comprises a mouse transmembrane domain and a mouse cytoplasmic domain.
8. The genetically modified mouse of claim 1, wherein the mouse comprises a cell that expresses an IL-6R α that comprises a human ectodomain on the surface of the cell.
9. A genetically modified mouse, comprising a humanization of an endogenous mouse IL-6R α gene, wherein the humanization comprises a replacement of mouse IL-6R α ectodomain-encoding sequence with human IL-6R α ectodomain-encoding sequence at the endogenous mouse IL-6R α locus, and wherein the humanized IL-6R α gene is under control of endogenous mouse regulatory elements.
10. The genetically modified mouse of claim 9, wherein a contiguous mouse sequence comprising mouse exons 1 through 8 is replaced with a contiguous genomic fragment of human IL-6R α sequence encoding a human IL-6R α ectodomain.
11. The genetically modified mouse of claim 10, wherein the contiguous genomic fragment of human IL-6R α sequence encoding the ectodomain is found in the CTD-2192J23 bacterial artificial chromosome.
12. The genetically modified mouse of claim 9, further comprising a humanized IL-6 gene comprising a replacement at an endogenous mouse IL-6 locus of a mouse gene encoding IL-6 with a human gene encoding human IL-6.

13. The genetically modified mouse of claim 12, wherein the humanized IL-6 gene is under control of endogenous mouse regulatory elements.
14. A method for making a humanized mouse, comprising replacing a mouse gene sequence encoding mouse IL-6 with a human gene encoding human IL-6 so that the human IL-6 gene is under control of endogenous mouse regulatory elements.
15. A method for making a humanized mouse, comprising replacing all mouse exons encoding ectodomain sequences of mouse 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 mouse regulatory elements.
16. A genetically modified mouse comprising a humanized IL-6R α gene comprising a replacement of mouse ectodomain encoding sequence with human ectodomain sequence, wherein the humanized IL-6R α gene comprises a mouse transmembrane sequence and a mouse cytoplasmic sequence; wherein the mouse 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 mouse regulatory elements.
17. The genetically modified mouse of claim 16, wherein the mouse does not express a mouse IL-6R α and does not express a mouse IL-6.