

WHAT IS CLAIMED IS:

1. A genetically modified ~~rodent~~mouse whose genome comprises:

(1) a humanized interleukin-1 receptor-like 2 (Il1rl2) gene ~~at an endogenous rodent Il1rl2 locus~~, wherein the humanized Il1rl2 gene

(i) encodes a humanized Il1rl2 protein that comprises an ectodomain substantially identical with the ectodomain of a human IL1RL2 protein and the transmembrane-cytoplasmic domains of a mouse Il1rl2 protein;

(ii) results from a replacement of a genomic fragment of an endogenous mouse Il1rl2 gene encoding the ectodomain of a human IL1RL2 protein; an endogenous mouse Il1rl2 protein with a nucleotide sequence of a human IL1RL2 gene encoding the ectodomain of the humanized IL1rl2 protein; and

(iii) is operably linked to the endogenous mouse Il1rl2 promoter;

(2) a human interleukin-1 family member 6 (IL1F6) gene ~~at an~~which replaces the endogenous ~~rodent~~mouse Il1f6 ~~locus~~gene;

(3) a human interleukin-1 family member 8 (IL1F8) gene ~~at an~~which replaces the endogenous ~~rodent~~mouse Il1f8 ~~locus~~gene; and

(4) a human interleukin-1 family member 9 (IL1F9) gene ~~at an~~which replaces the endogenous ~~rodent~~mouse Il1f9 ~~locus~~gene;

wherein the mouse expresses the humanized Il1rl2 protein, human IL1F6, human IL1F8, and human IL1F9.

2. The genetically modified ~~rodent~~mouse of claim 1, wherein the humanized Il1rl2 protein comprises ~~a transmembrane-cytoplasmic sequence substantially identical with the transmembrane-cytoplasmic sequence of the endogenous rodent Il1rl2 protein.~~

3. ~~The genetically modified rodent of claim 1 or 2, wherein the humanized Il1rl2 protein comprises a signal peptide substantially identical with the signal peptide of the endogenous rodent Il1rl2 protein.~~

4. ~~The genetically modified rodent of any one of claims 1-3, wherein the human IL1RL2 protein comprises the amino acid sequence as set forth in SEQ ID NO: 2.~~

5. ~~—The genetically modified rodent of any one of claims 1-3, wherein the ectodomain of the humanized Il1rl2 protein comprises amino acids 22-337 of SEQ ID NO: 7.~~

6. ~~The genetically modified rodent of any one of claims 1-3, wherein the humanized Il1rl2 protein comprises the amino acid sequence as set forth in SEQ ID NO: 7.~~

73. The genetically modified ~~rodent~~mouse of ~~any one of claims~~claim 1-6, wherein the humanized Il1rl2 gene ~~is operably linked to~~comprises exons 1-2 of the endogenous ~~rodent~~mouse Il1rl2 ~~promoter at~~gene, exons 3-8 of the human IL1RL2gene, and exons 9-11 of the endogenous ~~rodent~~mouse Il1rl2 ~~locus~~gene.

8. ~~4.~~ The genetically modified ~~rodent~~mouse of ~~any one of claims~~claim 1-7, wherein the mouse is homozygous for the humanized Il1rl2 gene, human IL1F6 gene, human IL1F8 gene and human IL1F9 gene.

5. A method of making a genetically modified mouse, comprising

(A) modifying a mouse genome to comprise

(1) a humanized interleukin-1 receptor-like 2 (Il1rl2) gene which

(i) encodes a humanized Il1rl2 protein that comprises the ectodomain of a human IL1RL2 protein and the transmembrane-cytoplasmic domains of a mouse Il1rl2 protein;

(ii) results from a replacement of a genomic fragment of ~~the an~~ endogenous ~~rodent~~mouse Il1rl2 gene ~~at~~encoding the ectodomain of an endogenous ~~rodent~~mouse Il1rl2 ~~locus~~protein with a nucleotide sequence of a human IL1RL2 gene: encoding the ectodomain of the humanized IL1rl2 protein; and

(iii) is operably linked to the endogenous mouse Il1rl2 promoter;

(2) a human interleukin-1 family member 6 (IL1F6) gene, which replaces the endogenous mouse Il1f6 gene;

(3) a human interleukin-1 family member 8 (IL1F8) gene, which replaces the endogenous mouse Il1f8 gene; and

(4) a human interleukin-1 family member 9. ~~—The~~ (IL1F9) gene, which replaces the endogenous mouse Il1f9 gene; and

(B) making a genetically modified ~~rodent~~mouse comprising the modified genome, wherein the mouse expresses the humanized Il1rl2 protein, human IL1F6, human IL1F8, and human IL1F9.

6. The method of claim 85, wherein the mouse genome is modified by a process comprising

(i) making a first mouse comprising the humanized Il1rl2 gene;

(ii) making a second mouse comprising the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene; and

(iii) crossing the first mouse with the second mouse to obtain the modified mouse genome.

7. The method of claim 6, wherein the mouse comprising the humanized Il1rl2 gene is made by providing a mouse embryonic stem (ES) cell,

replacing a genomic fragment of the endogenous mouse Il1rl2 gene of the mouse ES cell with the nucleotide sequence of the human IL1RL2 gene encoding the ectodomain of the humanized IL1rl2 protein, thereby obtaining a mouse ES cell comprising the humanized Il1rl2 gene, and

making a mouse using the mouse ES cell comprising the humanized Il1rl2 gene.

8. The method of claim 7, wherein the nucleotide sequence of a human IL1RL2 gene is a genomic fragment of the human IL1RL2 gene that ~~encodes substantially the ectodomain~~comprises exons 3-8 of the human IL1RL2 ~~protein~~gene.

109. The ~~genetically modified rodent~~method of claim 96, wherein the ~~genomic fragment of the human IL1RL2 gene comprises exons 3-8 of the human IL1RL2 gene.~~

11. The ~~genetically modified rodent of any one of claims 8-10, wherein the genomic sequence of the endogenous rodent Il1rl2 gene remaining after the replacement comprises the exons downstream of exon 8 of the endogenous rodent Il1rl2 gene.~~

12. The ~~genetically modified rodent of any one of claims 8-11, wherein the genomic sequence of the endogenous rodent Il1rl2 gene remaining after the replacement comprises exons 1-2 of the endogenous rodent Il1rl2 gene.~~

13. — ~~The genetically modified rodent of claim 8, wherein the humanized *IL1rl2* gene comprises exons 1-2 of the endogenous rodent *IL1rl2* gene, exons 3-8 of the human *IL1RL2* gene, and the remaining exons downstream of exon 8 of the endogenous rodent *IL1rl2* gene.~~
14. — ~~The genetically modified rodent of any of the preceding claims, wherein the human *IL1F6* gene replaces the endogenous rodent *IL1f6* gene at the endogenous rodent *IL1f6* locus.~~
15. — ~~The genetically modified rodent of any of the preceding claims, wherein the human *IL1F8* gene replaces the endogenous rodent *IL1f8* gene at the endogenous rodent *IL1f8* locus.~~
16. — ~~The genetically modified rodent of any of the preceding claims, wherein the human *IL1F9* gene replaces the endogenous rodent *IL1f9* gene at the endogenous rodent *IL1f9* locus.~~
17. — ~~The genetically modified rodent of any of the preceding claims, wherein the rodent is homozygous for each of the humanized *IL1rl2* gene, human *IL1F6* gene, human *IL1F8* gene and human *IL1F9* gene.~~
18. — ~~The genetically modified rodent of claim 20, wherein the rodent displays shortened colon as compared to a wild type rodent.~~
19. — ~~The genetically modified rodent of any of the preceding claims, wherein the rodent is a mouse or a rat.~~
20. — ~~A method of making a genetically modified rodent, comprising~~
— ~~modifying a rodent genome to comprise~~
— ~~(1) a humanized *IL1rl2* gene at an endogenous rodent *IL1rl2* locus, wherein the humanized *IL1rl2* gene encodes a humanized *IL1rl2* protein that comprises an ectodomain substantially identical with the ectodomain of a human *IL1RL2* protein;~~
— ~~(2) a human *IL1F6* gene at an endogenous rodent *IL1f6* locus;~~
— ~~(3) a human *IL1F8* gene at an endogenous rodent *IL1f8* locus; and~~
— ~~(4) a human *IL1F9* gene at an endogenous rodent *IL1f9* locus; and~~
— ~~making a rodent comprising the modified genome.~~
21. — ~~The method of claim 20, wherein the rodent genome is modified by a process comprising~~

——(i) making a first rodent comprising the humanized *IL1rl2* gene at the endogenous rodent *IL1rl2* locus;

——(ii) making a second rodent comprising the human *IL1F6* gene at the endogenous rodent *IL1f6* locus, the human *IL1F8* gene at the endogenous rodent *IL1f8* locus, and the human *IL1F9* gene at the endogenous rodent *IL1f9* locus; and

——(iii) crossing the first rodent with the second rodent to obtain the modified rodent genome.

22.——The method of claim 21, wherein the rodent comprising the humanized *IL1rl2* gene at the endogenous rodent *IL1rl2* locus is made by

——providing a rodent embryonic stem (ES) cell,

——inserting a nucleotide sequence of a human *IL1RL2* gene into the rodent *IL1rl2* locus of the rodent ES cell to form the humanized *IL1rl2* gene at the rodent *IL1rl2* locus, thereby obtaining a rodent ES cell comprising the humanized *IL1rl2* gene, and

——making a rodent using the rodent ES cell comprising the humanized *IL1rl2* gene.

23.——The method of claim 22, wherein the nucleotide sequence of a human *IL1RL2* gene replaces a genomic fragment of the rodent *IL1rl2* gene at the rodent *IL1rl2* locus.

24.——The method of claim 23, wherein the nucleotide sequence of a human *IL1RL2* gene is a genomic fragment of the human *IL1RL2* gene that encodes substantially the ectodomain of the human *IL1RL2* protein.

25.——The method of claim 24, wherein the genomic fragment of the human *IL1RL2* gene comprises exons 3-8 of the human *IL1RL2* gene.

26.——The method of any one of claims 23-25, wherein the genomic sequence of the endogenous rodent *IL1rl2* gene remaining after the replacement comprises the exons downstream of exon 8 of the endogenous rodent *IL1rl2* gene.

27.——The method of any one of claims 23-26, wherein the genomic sequence of the endogenous rodent *IL1rl2* gene remaining after the replacement comprises exons 1-2 of the endogenous rodent *IL1rl2* gene.

28. ~~The method of claim 22, wherein the humanized *IL1rl2* gene comprises exons 1-2 of the endogenous rodent *IL1rl2* gene, exons 3-8 of the human *IL1RL2* gene, and the remaining exons downstream of exon 8 of the endogenous rodent *IL1rl2* gene.~~

29. ~~The method of claim 21, wherein the second rodent mouse~~ comprising the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene is made by:

providing a ~~rodent mouse~~ embryonic stem (ES) cell,

~~inserting/replacing:~~

- ~~(i) the endogenous mouse *Il1f6* gene with the human IL1F6 gene into the rodent *Il1f6* locus of,~~
- ~~(i) the rodent ES cell,~~
- ~~(ii) endogenous mouse *Il1f8* gene with the human IL1F8 gene into, and~~
- ~~(ii) the rodent *Il1f8* locus of endogenous mouse *Il1f9* gene with the rodent ES cell, and~~
- ~~(iii) the human IL1F9 gene into the rodent *Il1f9* locus of the rodent ES cell,~~
thereby obtaining a ~~rodent mouse~~ ES cell comprising the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene, and

making the second ~~rodent mouse~~ using the ~~rodent mouse~~ ES cell comprising the human IL1F6 gene, the human IL1F8 gene, and the human ~~*IL1F9*~~IL1F9 gene.

~~3010.~~ The method of claim ~~299~~, wherein the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene, are provided in a contiguous nucleic acid molecule.

~~31. The method of any of claims 20-3011. An isolated cell or tissue obtained from the mouse of claim 1, wherein the isolated cell or tissue comprises the humanized *Il1rl2* gene, the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene.~~

12. An isolated mouse embryonic stem (ES) cell whose genome comprises:

(1) a humanized interleukin-1 receptor-like 2 (*Il1rl2*) gene, wherein the humanized *Il1rl2* gene

(i) encodes a humanized *Il1rl2* protein that comprises the ectodomain of a human *IL1RL2* protein and the transmembrane-cytoplasmic domains of a mouse *Il1rl2* protein;

_____ (ii) results from a replacement of a genomic fragment of an endogenous mouse *Il1rl2* gene encoding the ectodomain of an endogenous mouse *Il1rl2* protein with a nucleotide sequence of a human *IL1RL2* gene encoding the ectodomain of the humanized *IL1rl2* protein; and

_____ (iii) is operably linked to the endogenous mouse *Il1rl2* promoter;

_____ (2) a human interleukin-1 family member 6 (*IL1F6*) gene, which replaces the endogenous ~~rodent~~mouse *Il1f6* gene at the endogenous rodent *Il1f6* locus.;

32. _____ The method of any of claims 20-31, wherein the human *IL1F8* gene replaces the endogenous rodent *Il1f8* gene at the endogenous rodent *Il1f8* locus.

33. The method of any of claims 20-32, wherein the human *IL1F9* gene _____ (3) a human interleukin-1 family member 8 (*IL1F8*) gene, which replaces the endogenous ~~rodent~~*Il1f9* gene at the endogenous rodent *Il1f9* locus;mouse *Il1f8* gene; and

34. _____ An isolated cell or tissue of a rodent of any one of claims 1-19.

35. _____ A rodent embryonic stem (ES) cell comprising

_____ (1) a humanized *Il1rl2* gene at an endogenous rodent *Il1rl2* locus, wherein the humanized *Il1rl2* gene encodes a humanized *Il1rl2* protein that comprises an ectodomain substantially identical with the ectodomain of a human *IL1RL2* protein;

_____ (2) a human *IL1F6* gene at an endogenous rodent *Il1f6* locus;

_____ (3) a human *IL1F8* gene at an endogenous rodent *Il1f8* locus; and

(4) a human interleukin-1 family member 9 (*IL1F9*) gene at an, which replaces the endogenous ~~rodent~~mouse *Il1f9* locusgene.

36. _____ Use of the rodent ES cell of claim 35 in making a rodent.

37. _____ Use of a rodent of any one of claims 1-19 as a rodent model of diseases associated with deregulated *IL-36* signaling.

3813. A method of ~~assessing the therapeutic efficacy of a candidate~~determining whether a compound ~~for treating a disease associated with deregulated *IL-36* signaling~~is capable of inhibiting inflammation, the method comprising:

_____ providing a rodent of any one of claims 1-19,

administering an agent to the ~~rodent~~mouse of claim 1 to induce inflammation,
administering ~~a candidate~~the compound to the ~~rodent~~mouse, and
determining whether the ~~candidate~~ compound inhibits ~~induced~~ inflammation in the mouse.

~~39~~14. The method of claim ~~38~~13, wherein the ~~agent is DSS or oxazolone and~~ intestinal inflammation is induced in the ~~rodent~~.

~~40.~~—The method of claim 38, wherein the agent is IMQ and skin inflammation is induced in the ~~rodent~~.

~~41. The method of any one of claims 38-40, wherein the candidate~~ mouse by administering dextran sulfate sodium (DSS) or oxazolone to the mouse, and wherein the compound is administered to the rodent before, during, or after the administration of ~~the agent. DSS or oxazolone.~~

~~42. The method of any one of claims 38-41, wherein the candidate~~ 15. The method of claim 13, wherein the skin inflammation is induced in the mouse by administering imiquimod (IMQ), and wherein the compound is administered to the rodent before, during, or after the administration of IMQ.

16. The method of claim 13, wherein the compound is a small molecule compound, a nucleic acid inhibitor, or an antibody.

~~43~~17. The method of claim ~~42~~16, wherein the ~~candidate~~ compound is an antibody.

~~44.~~—18. The method of claim 5, wherein the humanized Il1rl2 protein comprises the amino acid sequence as set forth in SEQ ID NO: 7.

19. The method of claim 5, wherein the humanized Il1rl2 gene comprises exons 1-2 of the endogenous mouse Il1rl2 gene, exons 3-8 of the human IL1RL2gene, and exons 9-11 of the endogenous mouse Il1rl2 gene.

20. The isolated mouse ES cell of claim 12, wherein the humanized Il1rl2 protein comprises the amino acid sequence as set forth in SEQ ID NO: 7.

21. The isolated mouse ES cell of claim 12, wherein the humanized *Il1rl2* gene comprises exons 1-2 of the endogenous mouse *Il1rl2* gene, exons 3-8 of the human *IL1RL2* gene, and exons 9-11 of the endogenous mouse *Il1rl2* gene.

22. A mouse embryo, comprising the isolated mouse ES cell of claim 12.

23. A ~~targeting nucleic acid construct~~ mouse embryo, comprising the isolated mouse ES cell of claim 20.

~~——— a nucleotide~~ 24. A mouse embryo, comprising the isolated mouse ES cell of claim 21.

25. The method of claim 13, wherein the humanized *Il1rl2* protein comprises the amino acid sequence of a human *IL1RL2* gene, flanked by 5' and 3' rodent nucleotide sequences capable of mediating homologous recombination and integration as set forth in SEQ ID NO: 7.

26. The method of the nucleotide sequence of a human *IL1RL2* gene into a rodent *Il1rl2* locus to form a humanized *Il1rl2* gene claim 13, wherein the humanized *Il1rl2* gene encodes a comprises exons 1-2 of the endogenous mouse *Il1rl2* gene, exons 3-8 of the human *IL1RL2* gene, and exons 9-11 of the endogenous mouse *Il1rl2* gene.

27. The method of claim 13, wherein the mouse is homozygous for the humanized *Il1rl2* protein that comprises an ectodomain substantially identical with the ectodomain of a human *IL1RL2* protein.

~~45. — A targeting nucleic acid construct, comprising~~

~~——— a contiguous nucleic acid sequence comprising a~~ gene, human *IL1F6* gene, a human *IL1F8* gene, and a human *IL1F9* gene,

~~——— wherein the contiguous nucleic acid sequence is flanked by 5' and 3' rodent nucleotide sequences capable of mediating homologous recombination and integration of the contiguous nucleic acid sequence into the rodent locus encompassing the rodent *Il1f6* gene, the rodent *Il1f8* gene, and the rodent *Il1f9* gene.~~