

WHAT IS CLAIMED IS:

1. A genetically modified mouse 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 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 (IL1F9) gene which replaces the endogenous mouse Il1f9 gene;wherein the mouse expresses the humanized Il1rl2 protein, human IL1F6, human IL1F8, and human IL1F9.
2. The genetically modified mouse of claim 1, wherein the humanized Il1rl2 protein comprises the amino acid sequence as set forth in SEQ ID NO: 7.
3. The genetically modified mouse of claim 1, 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.
4. The genetically modified mouse of claim 1, 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 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 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 (IL1F9) gene, which replaces the endogenous mouse Il1f9 gene; and

(B) making a genetically modified 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 5, 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 comprises exons 3-8 of the human IL1RL2 gene.

9. The method of claim 6, wherein the second mouse comprising the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene is made by:

providing a mouse embryonic stem (ES) cell,

replacing:

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

making the second mouse using the mouse ES cell comprising the human IL1F6 gene, the human IL1F8 gene, and the human IL1F99 gene.

10. The method of claim 9, wherein the human IL1F6 gene, the human IL1F8 gene, and the human IL1F9 gene, are provided in a contiguous nucleic acid molecule.

11. 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 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 (IL1F9) gene, which replaces the endogenous mouse Il1f9 gene.

13. A method of determining whether a compound is capable of inhibiting inflammation, the method comprising:

administering an agent to the mouse of claim 1 to induce inflammation,
administering the compound to the mouse, and
determining whether the compound inhibits inflammation in the mouse.

14. The method of claim 13, wherein the intestinal inflammation is induced in the 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 DSS or oxazolone.

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.

17. The method of claim 16, wherein the compound is an antibody.

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 IL1RL2 gene, 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 mouse embryo, comprising the isolated mouse ES cell of claim 20.
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 as set forth in SEQ ID NO: 7.
26. The method of claim 13, 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.
27. The method of claim 13, wherein the mouse is homozygous for the humanized Il1rl2 gene, human IL1F6 gene, human IL1F8 gene and human IL1F9 gene.