

CLAIMS

1. A transgenic swine, comprising one or more nucleotide sequences encoding one or more HLA I polypeptides and/or one or more HLA II polypeptides inserted into one or more native SLA loci of the pig genome.
- 5 2. The transgenic swine of claim 1, wherein the one or more nucleotide sequences encode HLA I polypeptides inserted into a native SLA I locus.
3. The transgenic swine of claim 2, wherein the SLA I locus is selected from the group consisting of SLA-1 and SLA-2.
4. The transgenic swine of claim 2, wherein the HLA I polypeptides comprise HLA-A2
10 fused to human beta-2 microglobulin (B2M).
5. The transgenic swine of claim 2-4, wherein the one or more nucleotide sequences are inserted behind a native SLA I promoter.
6. The transgenic swine of claim 2-4, wherein the one or more nucleotide sequences are inserted at the intron 1/exon 2 junction of the SLA I locus.
- 15 7. The transgenic swine of claims 2-6, wherein the one or more nucleotide sequences further encode HLA II polypeptides inserted into the native SLA-DQ α locus.
8. The transgenic swine of claim 1, wherein the one or more nucleotide sequences encode HLA II polypeptides inserted into the native SLA-DQ α locus.
9. The transgenic swine of claims 7-8, wherein the HLA II polypeptides comprise the
20 HLA-DQ8 polypeptides.
10. The transgenic pig of claim 10, wherein the HLA-DQ8 polypeptides are targeted to the native SLA-DQ α locus through a bicistronic vector encoding HLA-DQ8 (HLA-DQA1:03:01:01 and HLA-DQB1:03:02:01).
11. The transgenic swine of claim 10, wherein the bicistronic vector further comprises a
25 high-efficiency IRES element.
12. The transgenic swine of claims 7-11, wherein the one or more nucleotide sequences encoding the HLA II polypeptides are inserted behind the native SLA DQ α promoter.
13. The transgenic swine of claims 7-11, wherein the one or more nucleotide sequences encoding the HLA II polypeptides are inserted at the intron 1/exon 2 junction of the
30 SLA DQ α locus.
14. The transgenic swine of claim 1, wherein the HLA I polypeptides are selected from the group consisting of HLA-A, HLA-A2, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G, and wherein the HLA II polypeptides are selected from the group consisting of HLA-DP, HLA-DM, HLA-DO, HLA-DQ, and HLA-DR.

15. A method of xenotransplantation of thymic tissue into a subject in need thereof, comprising the introduction of thymic tissue from the transgenic swine according to any of claims 1-14 into the subject.
16. A method of recovering or restoring impairment of the function of the thymus in a
5 subject in need thereof, comprising the introduction of thymic tissue from the transgenic swine according to any of claims 1-14 into the subject.
17. A method of reconstituting T cells in a subject in need thereof, comprising the introduction of thymic tissue from the transgenic swine according to any of claims 1-13 into the subject.
- 10 18. The methods of claims 15-17, wherein the subject is a human.
19. The method of claims 15-18, wherein the transgenic swine comprises HLA polypeptides derived from the subject.
20. A method of producing a transgenic swine of any of claims 1-14, comprising administering at least one targeting vector and at least one CRISPR-Cas9 plasmid into
15 a swine cell, wherein the targeting vector comprises one or more nucleotide sequences encoding one or more HLA I polypeptides and/or one or more HLA II polypeptides.
21. The method of claim 20, wherein the one or more nucleotide sequences encoding one or more HLA I polypeptides and/or one or more HLA II polypeptides derive from a specific individual subject.
- 20 22. A method of generating a human immune system (HIS) mouse, comprising thymectomizing the mouse and introducing swine fetal thymic tissue and human CD34+ cells into the mouse.
23. The method of claim 22, wherein the human CD34+ cells are fetal or adult.
24. The method of claim 22, wherein the human CD34+ cells are derived from cord
25 blood.
25. A method of generating a human immune system (HIS) mouse, comprising thymectomizing the mouse and introducing swine fetal thymic tissue, wherein the fetal thymic tissue is derived from the transgenic swine of claims 1-14.