Claims

What is claimed is:

1. A method of producing an allogeneic cultured postnatal thymus tissue-derived product suitable for implantation into a human, comprising the steps of:

subjecting donor thymus to a conditioning regimen for a period from about 6 days to about 21 days; wherein the conditioning regimen for the donor thymus tissue comprises aseptically processing the donor thymus tissue in a thymus organ medium to produce partially T-cell depleted donor thymus tissue slices;

detecting increasing levels of CCL21 in the thymus organ medium during the conditioning regimen; and

recovering the partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product suitable for implantation.

2. The method according to claim 1:

(i) further comprising cryopreserving the allogeneic cultured postnatal thymus tissue-derived product in liquid nitrogen for future implantation;

(ii) further comprising detecting decreasing levels of one or more of L-selectin, M-CSF, galectin-7 and IL-16 in the thymus organ medium during the conditioning regimen;

(iii) further comprising detecting increasing levels of one or more of CXCL12, CXCL16 and CCL11 in the thymus organ medium during the conditioning regimen;

(iv) wherein the conditioning regimen is for six days, or seven days, or eight days, or nine days, or 10 days, or 11 days, or 12 days, or 13 days, or 14 days, or 15 days, or 16 days, or 17 days , or 18 days or 19 days, or 20 days, or 21 days; or for a period of 5-6 days, or 5-7 days, or 5-8 days, or 5-9 days, or 5-10 days, or 6 to 7 days, or 6 to 8 days, or 6 to 9 days, or 6 to 10 days, or 6 to 11 days, or 6 to 12 days, or 6 to 21 days, or 7 to 21 days, or 8 to 21 days, or 9 to 21 days, or 10 to 21 days, or 11 to 21 days, or 12 to 21 days, 13 to 21 days or 14 to 21 days, or 15 to 21 days, or 16 to 21 days or 17 to 21 days or 18 to 21 days, or 19 to 21 days, or 20 to 21 days; and/or

(v) further comprising identifying, during the conditioning regimen, areas positive for keratin AE1/AE3 scattered throughout the donor thymus tissue slices, the presence of at least one Hassall body, CK14 staining scattered throughout the donor thymus tissue slices, and the presence of intact nuclei.

3. A method of producing an allogeneic cultured postnatal thymus tissue-derived product suitable for implantation into a human, comprising the steps of:

subjecting donor thymus to a conditioning regimen for a period from about 6 days to about 21 days; wherein the conditioning regimen for the donor thymus tissue comprises aseptically processing the donor thymus tissue in a thymus organ medium to produce partially T-cell depleted donor thymus tissue slices;

detecting, in the thymus organ medium during the conditioning regimen, the levels of at least one biomarker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF

R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40, RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1; and

recovering the partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product suitable for implantation.

4. A method for determining whether allogeneic cultured postnatal thymus tissue-derived product is suitable for implantation into a human, the method comprising the steps of:

conditioning donor thymus tissue slices in a thymus organ medium for a period of about 6 days to about 21 days; wherein the conditioning regimen for the donor thymus tissue comprises aseptically processing the donor thymus tissue in the thymus organ medium to produce partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product suitable for implantation; and

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, M-CSF, galectin-7, IL-16, CCL21, CXCL12, CXCL16, and CCL11.

5. A method for determining whether allogeneic cultured postnatal thymus tissue-derived product is suitable for implantation into a human, the method comprising the steps of:

conditioning donor thymus tissue slices in a thymus organ medium for a period of about 6 days to about 21 days; wherein the conditioning regimen for the donor thymus tissue comprises aseptically processing the donor thymus tissue in the thymus organ medium to

produce partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product suitable for implantation; and

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40, RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1.

6. Allogeneic cultured postnatal thymus tissue-derived product for use in therapy, the allogeneic cultured postnatal thymus tissue-derived product produced by:

subjecting donor thymus tissue slices to a conditioning regimen in a thymus organ medium for a period of about 6 days to about 21 days; wherein the conditioning regimen comprises aseptically processing the donor thymus tissue in the thymus organ medium to produce partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product; and

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40,

RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1.

7. The allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to claim 6, wherein the therapy is treating a thymic disorder in a subject.

8. The allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to claim 7, wherein the thymic disorder is:

(i) congenital athymia associated with complete DiGeorge syndrome;

(ii) congenital athymia associated with 22q11.2 deletion;

(iii) congenital athymia associated with CHARGE (coloboma, heart defect, choanal atresia, growth or mental retardation, genital hypoplasia and ear anomalies or deafness);

(iv) congenital athymia associated with mutations in the chd7 (chromodomain-helicase-DNA-binding protein 7) gene;

(v) congenital athymia associated with forkhead box protein N1 (FOXN1) deficiency;

(vi) congenital athymia associated with mutations in the TBX-1 or TBX-2 gene;

(vii) age-related thymic involution;

(viii) associated with a thymoma;

(ix) associated with a thymoma and wherein the thymoma is malignant;

(x) associated with a thymoma and wherein the thymoma is non-malignant; or

(xi) associated with myasthenia gravis (MG), pure red cell aplasia and hypogammaglobulinemia.

9. The method according to claim 4 or the allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any of claims 6-8, wherein:

(i) the at least one marker is L-selectin; or

(ii) the at least one marker is L-selectin and the levels of L-selectin in the thymus organ medium decrease during the conditioning regimen.

10. The method according to claim 4 or the allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any of claims 6-9, wherein:

(i) the at least one marker is CCL21; or

(ii) the at least one marker is CCL21 and the levels of CCL21 in the thymus organ medium increase during the conditioning regimen.

11. The method according to claim 4 or the allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any of claims 6-10, wherein:

(i) the at least one marker is CXCL12; or

(ii) the at least one marker is CXCL12 and the levels of CXCL12 in the thymus organ medium increase during the conditioning regimen.

12. Allogeneic cultured postnatal thymus tissue-derived product for use in therapy to provide immune-competence in a human subject by implanting the allogeneic cultured postnatal thymus tissue-derived product into the human subject, the allogeneic cultured postnatal thymus tissue-derived product produced by:

conditioning donor thymus tissue slices in a thymus organ medium for a period of about 6 days to about 21 days; wherein the conditioning regimen comprises aseptically processing the donor thymus tissue in the thymus organ medium to produce partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product;

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40, RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1.

13. Allogeneic cultured postnatal thymus tissue-derived product for use in therapy to provide immune-competence in a human subject undergoing a solid organ transplant by implanting the solid organ; and implanting the allogeneic cultured postnatal thymus tissue-derived product into the human subject, the allogeneic cultured postnatal thymus tissue-derived product produced by:

removing the thymus of the human subject;

obtaining thymus tissue from a donor matching HLA-Class I and HLA-Class II alleles in the solid organ;

slicing the donor thymus;

conditioning the donor thymus tissue slices in a thymus organ medium for a period of about 6 days to about 21 days; wherein the conditioning regimen comprises aseptically processing the donor thymus tissue in the thymus organ medium to produce partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product; and

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40, RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1.

14. Allogeneic cultured postnatal thymus tissue-derived product for use in therapy to promote donor-specific tolerance to an allogeneic solid organ transplant obtained from a deceased donor, in a recipient in need of a solid organ transplant, by implanting the allogeneic cultured postnatal thymus tissue-derived product into the recipient, after up to 21 days of conditioning regimen,

wherein the dosage of allogeneic cultured postnatal thymus tissue-derived product is about 1,000 - 22,000 mm^2 of allogeneic cultured postnatal thymus tissue-derived product surface area / recipient body surface area in m^2, and

further wherein the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient,

the allogeneic cultured postnatal thymus tissue-derived product produced by:

(a) removing the thymus of the recipient;

(b) treating the recipient with an induction immunosuppressive regimen comprising one or more immunosuppressive agents to deplete the recipient's T cells and/or to suppress the recipient's T cells from rejecting the transplanted solid organ;

(c) providing both a suitable solid human organ and thymus tissue from a deceased donor;

(d) transplanting the solid human organ into the recipient;

(e) treating the recipient with a maintenance immunosuppressive regimen;

(f) providing an allogeneic cultured postnatal thymus tissue-derived product,

wherein donor thymus tissue slices are subjected to a conditioning regimen, wherein the conditioning regimen comprises aseptically processing the donor thymus tissue slices in the thymus organ medium for a period of about 6 days to about 21 days to produce partially T-cell depleted donor thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product; and

(g) detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40, RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1.

15. Allogeneic cultured postnatal thymus tissue-derived product for use in therapy to promote donor-specific tolerance to an allogeneic solid organ transplant obtained from a living human donor, in a human recipient in need of a solid organ transplant, the allogeneic cultured postnatal thymus tissue-derived product produced by processing thymus tissue from a thymus donor expressing HLA alleles matched to HLA-Class I and HLA-Class II alleles in the recipient that are not present in the solid organ transplant;

wherein donor thymus tissue slices were subjected to a conditioning regimen for up to about 21 days;

further wherein the conditioning regimen comprises aseptically processing the donor thymus tissue slices in a thymus organ medium to produce partially T-cell depleted thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product; and

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40, RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1;

the therapy comprising the steps of:

(a) removing the thymus of the recipient;

(b) treating the recipient with an induction immunosuppressive regimen comprising one or more immunosuppressive agents to deplete the recipient's T cells and/or to suppress the recipient's T cells from rejecting the transplanted solid organ;

(c) providing a suitable solid organ from a living human donor;

(d) transplanting the solid organ into the recipient;

(e) treating the recipient with a maintenance immunosuppressive regimen;

(f) providing a cryopreserved allogeneic cultured postnatal thymus tissue-derived product maintained in a cryopreserved allogeneic cultured postnatal thymus tissue-derived product bank;

(g) thawing the cryopreserved allogeneic cultured postnatal thymus tissue-derived product, and

(h) implanting the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product into the recipient,

wherein the dosage of the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product is about 1,000 - 22,000 mm^2 of allogeneic cultured postnatal thymus tissue-derived product surface area / recipient body surface area in m^2, and

further wherein the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient;

16. The allogeneic cultured postnatal thymus tissue-derived product according to claim 15, wherein:

(i) HLA matching permits minor variations in amino acid sequence of the alleles in the second field;

(ii) HLA matching permit mismatches for HLA-DP alleles in the second field;

(iii) about one-half of the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product is transplanted into the recipient and the remainder cryopreserved for future use; and/or

(iv) step (h) is performed about one month or more after the transplantation of the solid organ.

17. Allogeneic cultured postnatal thymus tissue-derived product for use in therapy to promote donor-specific tolerance to an allogeneic solid organ transplant obtained from a deceased human donor, in a human recipient in need of a solid organ transplant, wherein the allogeneic cultured postnatal thymus tissue-derived product is processed from thymus tissue from a thymus donor expressing HLA alleles matched to HLA alleles in the recipient that are not present in the solid organ transplant;

wherein donor thymus tissue slices were subjected to a conditioning regimen for up to about 21 days;

further wherein the conditioning regimen comprises aseptically processing the donor thymus tissue slices in a thymus organ medium to produce partially T-cell depleted thymus tissue slices as the allogeneic cultured postnatal thymus tissue-derived product,

detecting, in the thymus organ medium during the conditioning regimen, the level of at least one marker selected from L-selectin, CXCL16, M-CSF, CCL21/6Ckine, galectin-7, MIF, GDNF, CTACK, MIP-3b, ICAM-1, PECAM-1, IL-2Rg, SCF R, IL-16, GDF-15, PDGF-AA, CXCL12/SDFF-1a, MIP-3a, IL-2Ra, ICAM-3, LIGHT, IGFBP-1, BCMA, EGF R, uPAR, MIP-1b, PIGF, PF4, CCL11/Eotaxin, HVEM, IGFBP-6, IL-6R. IL-12p40,

RANTES, MICA, GCP-2, OPN, ALCAM, NRG1-B1, CEACAM-1, IL-1b, DKK-1 and ANG-1;

the therapy comprising the steps of:

(a) removing the thymus of the recipient;

(b) treating the recipient with an induction immunosuppressive regimen comprising one or more immunosuppressive agent to deplete the recipient's T cells and/or to suppress the recipient's T cells from rejecting the transplanted solid organ;

(c) providing a suitable solid organ from a living human donor;

(d) transplanting the solid organ into the recipient;

(e) treating the recipient with a maintenance immunosuppressive regimen;

(f) providing a cryopreserved allogeneic cultured postnatal thymus tissue-derived product maintained in a cryopreserved allogeneic cultured postnatal thymus tissue-derived product bank;

(g) thawing the cryopreserved allogeneic cultured postnatal thymus tissue-derived product; and

(h) implanting the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product into the recipient, wherein the dosage of the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product is about 1,000 - 22,000 mm^2 of allogeneic cultured postnatal thymus tissue-derived product surface area / recipient body surface area in m^2, and

further wherein the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient.

18. The allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any one of claims 13-17, wherein:

(i) the solid organ transplant is a heart transplant, a kidney transplant, a liver transplant, a lung transplant, a heart/lung transplant, a pancreas transplant, an intestine transplant, a stomach transplant, an abdominal wall transplant, a craniofacial transplant, a scalp transplant, a penile transplant, a uterus transplant, a unilateral or bilateral upper limb transplant, a unilateral vascularized composite allograft, or any combination thereof;

(ii) the solid organ transplant is a heart transplant;

(iii) the solid organ transplant is a heart transplant and the heart transplant is a pediatric heart transplant; or

(iv) the solid organ transplant is a heart transplant and the heart transplant is an adult heart transplant.

19. The method or the allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any one of claims 3-18, wherein the conditioning regimen is 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, or 21 days.

20. The method or the allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any one of claims 3-19, the method further comprising identifying, during the conditioning regimen, areas positive for keratin AE1/AE3 scattered throughout the donor thymus tissue slices, the presence of at least one Hassall body, CK14 staining scattered throughout the donor thymus tissue slices, and the presence of intact nuclei.

21. The method or the allogeneic cultured postnatal thymus tissue-derived product for use in therapy according to any one of claims 3-20, wherein the at least one marker is selected from L-selectin, M-CSF, galectin-7, IL-16, CCL21, CXCL12, CXCL16, or CCL11; and wherein the level is decreased if the marker is L-selectin, M-CSF, galectin-7, or IL-16 or wherein the level is increased if the marker is CCL21, CXCL12, CXCL16, or CCL11.