CLAIMS

1. An allogeneic cultured postnatal thymus tissue-derived product for use in a method for promoting donor-specific tolerance to an allogeneic solid organ transplant obtained from a deceased donor, in a recipient in need of a solid organ transplant,

in which the allogeneic cultured postnatal thymus tissue-derived product is prepared by obtaining suitable thymus tissue from the donor;

in which the donor thymus tissue is subjected to a conditioning regimen for a period up to 21 days to produce the allogeneic cultured postnatal thymus tissue-derived product;

in which 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;

in which the partially T-cell depleted donor thymus tissue slices show areas positive for cytokeratin (CK) (using antibody AE1/AE3) scattered throughout the tissue, the presence of at least one Hassall body, CK14 staining scattered throughout the tissue and presence of intact nuclei;

in which the method comprises the steps of:

(a) removal of 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 both a suitable solid human organ and a thymus gland from a deceased donor;

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

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

and

(f) implanting the allogeneic cultured postnatal thymus tissue-derived product into the recipient after 12 to 21 days of conditioning regimen, in which the dosage of thymus

tissue slices is 1,000 – 20,000 mm^2 of thymus tissue surface area / recipient body surface area in m^2, and further in which the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient.

2. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which the method further comprises the step of cryopreserving peripheral blood mononuclear cells from the deceased donor for future use in a mixed lymphocyte reaction to demonstrate cellular tolerance, optionally in which the mixed lymphocyte reaction to demonstrate cellular tolerance is performed using peripheral blood mononuclear cells from the recipient and cryopreserved peripheral blood mononuclear cells from the donor following the implantation of allogeneic cultured postnatal thymus tissue-derived product in accordance with step (f), preferably 6 to 12 months following the implantation of allogeneic cultured postnatal thymus tissue-derived product and more preferably after naïve T cells constitute about 10% of total T cells in the recipient.

3. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which:

(a) the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis in the subject within 12 months following the implantation of allogeneic cultured postnatal thymus tissue-derived product;

(b) the donor thymus, on the day of harvest, demonstrates that >50% of areas are positive for keratin in a lacy staining pattern, that Hassall bodies are present, that CK14 stains in a lacy pattern, and that >90% of nuclei are intact; or

(c) humoral tolerance is determined by the development of humoral immunity and the absence of donor reactive antibodies toward the MHC of the donor.

4. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which the induction immunosuppressive regimen comprises an immunosuppressive agent selected from the group of glucocorticoid, anti-thymocyte globulin (rabbit), anti-thymocyte globulin (equine), and alemtuzumab, optionally in which the induction immunosuppressive regimen comprises:

(a) rabbit-derived anti-thymocyte globulin, optionally in which the rabbit-derived anti-thymocyte globulin is administered intravenously in a dose of about 1.5 mg/kg/day for 3 to 7 days, preferably in which the anti-thymocyte globulin is administered daily for 3-14 days at about 15 mg/kg/day by intravenous administration; or

(b) alemtuzumab, optionally in which the alemtuzumab is administered at a dose of:

(i) about 0.25 mg/kg for 4 days intravenously for recipients less than 35 kg in body weight; or

(ii) 3 to 20 mg for 4 days intravenously for recipients more than 35 kg in body weight.

5. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which the maintenance immunosuppressive regimen comprises administration of:

(a) a glucocorticoid, in which the glucocorticoid comprises methylprednisolone sodium succinate, optionally, in which the methylprednisolone sodium succinate is administered intravenously at no greater than 4 mg/kg/day after implantation of allogeneic cultured postnatal thymus tissue-derived product;

(b) a glucocorticoid plus tacrolimus or cyclosporine, and further administering mycophenylate mofetil, an equivalent of mycophenylate mofetil or azathroprine;

(c) one or more immunosuppressive agent selected from the group consisting of a calcineurin inhibitor, and inosine monophosphate dehydrogenase inhibitor, or azathioprine optionally in which the calcineurin inhibitor is tacrolimus or cyclosporine A, or in which the inosine monophosphate dehydrogenase inhibitor is:

(i) mycophenolate mofetil, which is optionally administered orally or intravenously, preferably at a dose of 15 to 25 mg/kg two to three times per day; or

(ii) mycophenolic acid, which is optionally administered at a dose of 25 to 50 mg/kg in 2 or 3 doses per day; or

(d) a glucocorticoid selected from the group consisting of methylprednisolone, prednisone and prednisolone, optionally in which the glucocorticoid is administered in a tapered dosage reduction and the dose is kept at or below 4 mg/kg/day.

6. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which:

(a) the solid organ is a portion of a whole organ; or

(b) 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 combination thereof, optionally in which:

(i) the solid organ transplant is a heart transplant, which is optionally a paediatric heart transplant; or

(ii) the heart transplant is an adult heart transplant.

7. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, further comprising evaluating the recipient for HLA class I or HLA class II panel reactive antibodies ("PRA") score prior to transplanting the solid organ, optionally in which:

(a) if a PRA score of >20% virtual cross-match is recorded, the method will further comprise the step of performing plasmapheresis in the operating room at the time of solid organ transplant in the recipient; or

(b) if a PRA score of >70% virtual cross-match is recorded, the method will further comprise the step of performing an actual prospective donor cross-match and performing plasmapheresis in the operating room at the time of solid organ transplant in the recipient.

8. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which recipients with HLA antibodies are cross-matched with potential donors, optionally in which recipients with HLA antibodies are virtually cross-matched with UNET.

9. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which the solid organ is HLA-mismatched, optionally in which HLA-mismatched is determined by typing HLA alleles HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DQA1, HLA- DPB1, HLA-DPA1 in the donor and the recipient, and preferably in which HLA-mismatched comprises at least one of HLA alleles HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DQA1, HLA- DPB1, HLA-DPA1 is different between the donor and the recipient.

10. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which a portion of the allogeneic cultured postnatal thymus tissue-derived product is surgically implanted into the quadriceps thigh muscle of the recipient, optionally in which the remaining portion of the allogeneic cultured postnatal thymus tissue-derived product is cryopreserved in liquid nitrogen for future transplantation into the recipient.

11. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which the conditioning regimen is for a period of 12 days to 21 days, optionally in which the conditioning period is for about 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days.

12. An allogeneic cultured postnatal thymus tissue-derived product for use according to Claim 1, in which:

(a) the administration of the one or more immunosuppressive agent of the maintenance immunosuppressant regimen is weaned after naïve T cells reach 10% of total T cells; or

(b) the implanted allogeneic cultured postnatal thymus tissue-derived product is biopsied at 2 to 12 months post-implantation to assess for evidence of thymopoiesis by immunochemistry.

13. A cryopreserved allogeneic cultured postnatal thymus tissue-derived product, prepared by method comprising the steps of:

(a) typing HLA alleles: HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DQA1, HLA- DPB1, HLA-DPA1 in thymus tissue previously obtained from a donor;

(b) subjecting the thymus tissue to a conditioning regimen for a period up to 12 days; in which 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; further in which the donor thymus tissue slices show, on days 5 to 9, areas positive for keratin AE1/AE3 scattered throughout the tissue, the presence of at least one Hassall body, CK14 staining scattered throughout the tissue and presence of intact nuclei upon completion of the conditioning regimen;

(c) harvesting the partially T-cell depleted donor thymus tissue slices as allogeneic cultured postnatal thymus tissue-derived product;

(d) cryopreserving the allogeneic cultured postnatal thymus tissue-derived product in liquid nitrogen; and

(e) maintaining the cryopreserved allogeneic cultured postnatal thymus tissue-derived product in liquid nitrogen in a cryopreserved allogeneic cultured postnatal thymus tissue-derived product bank.

14. Use of an allogeneic cultured postnatal thymus tissue-derived product in the preparation of a medicament for promoting donor-specific tolerance to an allogeneic solid organ transplant obtained from a deceased donor, in a recipient in need of a solid organ transplant, in which the allogeneic cultured postnatal thymus tissue-derived product is obtained from suitable thymus tissue of the solid organ donor; in which the donor thymus tissue is subjected to a conditioning regimen for a period up to 21 days to produce allogeneic cultured postnatal thymus tissue-derived product; further in which 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; in which the partially T-cell depleted donor thymus tissue slices show areas positive for cytokeratin (CK) (using antibody AE1/AE3) scattered throughout the tissue, the presence of at least one Hassall body, CK14 staining scattered throughout the tissue and presence of intact nuclei; in which:

(a) the thymus of the recipient is to be removed;

(b) the recipient is to be treated 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) both a suitable solid human organ and a thymus gland from a deceased donor are to be provided;

(d) the solid human organ is to be transplanted into the recipient;

(e) the recipient is to be treated with a maintenance immunosuppressive regimen; and

(f) the allogeneic cultured postnatal thymus tissue-derived product is to be implanted into the recipient after 12 to 21 days of conditioning regimen, in which the dosage of thymus tissue slices is 1,000 – 20,000 mm^2 of thymus tissue surface area / recipient body surface area in m^2, and further in which the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient.

15. Use of an allogeneic cultured postnatal thymus tissue-derived product according to Claim 14, in which the allogeneic cultured postnatal thymus tissue-derived product is maintained in liquid nitrogen and cryopreserved for future use.

16. A cryopreserved allogeneic cultured postnatal thymus tissue-derived product, prepared by method comprising the steps of:

(a) obtaining suitable thymus tissue from a donor;

(b) typing HLA alleles: HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DQA1, HLA- DPB1, HLA-DPA1;

(c) subjecting the thymus tissue to a conditioning regimen for a period up to 12 days; in which 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; further in which the donor thymus tissue slices show, on days 5 to 9, areas positive for keratin AE1/AE3 scattered throughout the tissue, the presence of at least one Hassall body, CK14 staining scattered throughout the tissue and presence of intact nuclei upon completion of the conditioning regimen;

(d) harvesting the partially T-cell depleted donor thymus tissue slices as allogeneic cultured postnatal thymus tissue-derived product;

(e) cryopreserving the allogeneic cultured postnatal thymus tissue-derived product in liquid nitrogen; and

(f) maintaining the cryopreserved allogeneic cultured postnatal thymus tissue-derived product in liquid nitrogen in a cryopreserved allogeneic cultured postnatal thymus tissue-derived product bank.

17. Use of a cryopreserved allogeneic cultured postnatal thymus tissue-derived product maintained in a cryopreserved allogeneic cultured postnatal thymus tissue-derived product bank in the preparation of a medicament for promoting 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; in which the cryopreserved allogeneic cultured postnatal thymus tissue-derived product was 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; in which the donor thymus tissue was subjected to a conditioning regimen for a period up to 12 days; further in which 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 thymus tissue slices, in which the thymus tissue slices show areas positive for keratin AE1/AE3 scattered throughout the tissue, the presence of at least one Hassall body, CK14 staining scattered throughout the tissue and presence of intact nuclei upon completion of the conditioning regimen; in which:

(a) the thymus of the recipient is to be removed;

(b) the recipient is to be treated 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) a suitable solid organ from a living human donor is to be provided;

(d) the solid organ is to be transplanted into the recipient;

(e) the recipient is to be treated with a maintenance immunosuppressive regimen;

(f) the cryopreserved allogeneic cultured postnatal thymus tissue-derived product is to be thawed; and

(h) the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product is to be implanted into the recipient, in which the dosage of the cryopreserved allogeneic cultured postnatal thymus tissue-derived product is 1,000 – 20,000 mm^2 of thymus tissue surface area / recipient body surface area in m^2, and further in which the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient.

18. Use of a cryopreserved allogeneic cultured postnatal thymus tissue-derived product maintained in a cryopreserved allogeneic cultured postnatal thymus tissue-derived product bank in the manufacture of a medicament for promoting 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; in which the cryopreserved 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; in which the donor thymus tissue was subjected to a conditioning regimen for a period up to 12 days; further in which 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 thymus tissue slices, in which the thymus tissue slices show areas positive for keratin AE1/AE3 scattered throughout the tissue, the presence of at least one Hassall body, CK14 staining scattered throughout the tissue and presence of intact nuclei upon completion of the conditioning regimen; in which:

(a) the thymus of the recipient is to be removed;

(b) the recipient is to be treated 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) a suitable solid organ from a living human donor is to be provided;

(d) the solid organ is to be transplanted into the recipient;

(e) the recipient is to be treated with a maintenance immunosuppressive regimen;

(f) the cryopreserved allogeneic cultured postnatal thymus tissue-derived product is to be thawed; and

(h) the thawed cryopreserved allogeneic cultured postnatal thymus tissue-derived product is to be implanted into the recipient, in which the dosage of the cryopreserved allogeneic cultured postnatal thymus tissue-derived product is 1,000 – 20,000 mm^2 of thymus tissue surface area / recipient body surface area in m^2, and further in which the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient.