CLAIMS

1. 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 donor, in a recipient in need of a solid organ transplant,

in which the allogeneic cultured postnatal thymus tissue-derived product is to be 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, between days 5 and 9 of the conditioning regimen, show areas positive for cytokeratin (CK) staining, the presence of at least one Hassall body, and the presence of intact nuclei of thymic epithelial cells and other stromal cells;

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 agents 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 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 the partially T-cell depleted donor thymus tissue slices is 1,000 – 20,000 mm^2 of thymus tissue surface area / recipient body surface area in m^2, and in which the implanted

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

2. Use according to Claim 1, in which the method further comprises the step of cryopreserving peripheral blood mononuclear cells from the 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. 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) partially T-cell depleted donor thymus tissue slices, between days 5 and 9 of the conditioning regimen, show areas positive for cytokeratin 14 (CK 14) staining; 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. 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 to be 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 to be administered daily for 3-14 days at about 15 mg/kg/day by intravenous administration; or

(b) alemtuzumab, optionally in which the alemtuzumab is to be 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. Use according to Claim 1, in which, during the maintenance immunosuppressive regimen, the patient is to be administered with:

(a) a glucocorticoid, in which the glucocorticoid comprises methylprednisolone sodium succinate, optionally, in which the methylprednisolone sodium succinate is to be 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 in which mycophenylate mofetil, an equivalent of mycophenylate mofetil or azathroprine are to be administered;

(c) one or more immunosuppressive agents selected from the group consisting of a calcineurin inhibitor, and inosine monophosphate dehydrogenase inhibitor, and 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 to be 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 to be 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 to be administered in a tapered dosage reduction and the dose is kept at or below 4 mg/kg/day.

6. 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. 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 further comprising a step of plasmapheresis to be performed 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 further comprising a step of an actual prospective donor cross-match to be performed and plasmapheresis to be performed in the operating room at the time of solid organ transplant in the recipient.

8. 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. Use according to Claim 1, in which the solid organ is HLA-mismatched, optionally in which HLA-mismatching 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 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. Use according to Claim 1, in which a portion of the allogeneic cultured postnatal thymus tissue-derived product is to be 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. 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. Use according to Claim 1, in which:

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

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

13. Use according to Claim 1, in which the allogeneic cultured postnatal thymus tissue-derived product is maintained in liquid nitrogen and cryopreserved for future use.

14. 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 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 partially T-cell depleted thymus tissue slices show areas positive for CK staining, the presence of at least one Hassall body, and the presence of intact nuclei of

thymic epithelial cells and other stromal cells 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 agents 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 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

(g) 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 in which the implanted allogeneic cultured postnatal thymus tissue-derived product induces thymopoiesis and tolerance in the recipient.

15. A method of preparing a cryopreserved allogeneic cultured postnatal thymus tissue-derived product, the 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 partially T-cell depleted donor thymus tissue slices show areas positive for CK staining, the presence of at least one Hassall body, and the presence of intact nuclei of thymic epithelial cells and other stromal cells 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.

16. Use according to any of Claims 1 to 13, in which the partially T-cell depleted donor thymus tissue slices, between days 5 and 9 of the conditioning regimen, show areas positive for CK staining in a lacy pattern.

17. Use according to any of Claims 1 to 13 or 16, in which the partially T-cell depleted donor thymus tissue slices, between days 5 and 9 of the conditioning regimen, show areas positive for CK 14 staining in a lacy pattern.

18. Use according to Claim 14 or a method according to Claim 15, in which the partially T-cell depleted donor thymus tissue slices show areas positive for CK staining in a lacy pattern upon completion of the conditioning regimen.

19. Use according to Claim 14 or 18 or a method according to Claim 15 or 18, in which the partially T-cell depleted donor thymus tissue slices show areas positive for CK14 staining in a lacy pattern upon completion of the conditioning regimen.

20. Use according to any Claims 1 to 14 or 16 to 19, in which the solid organ transplant is obtained from a deceased donor.

21. Use according any of Claims 1 to 5, 7 to 14 and 16 to 19, in which the solid organ transplant is obtained from a living donor.