GENERATION OF TOLEROGENIC HUMAN DC THROUGH RAPAMYCIN CONDITIONING AND GENETIC MODIFICATION WITH HLA-G

A thesis submitted in partial fulfillment of the
PhD degree

in

The Department of Medicine
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by

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APPENDIX

Appendix 3.1

Table 1. Summary of the primer sequences used in the RT-PCR
- **Human**

Primer name	*Sequence*
HLA-G1SalIF	5’ GCGTCGACATGGTGGTCATGGCGCCCCGAACC
HLA-G1KpnIR	5’ GGGGTACCTCAATCTGAGCTCTTCTTTCTCCACAG
HLA-G5KpnIInt4R	5’ GGGGTACCTTAAAGGTCTTCAGAGAGGCTCCTGC
HLA-G_int_F	5’ GGGGAGGACCAGACCCAGGACG
HLA-G_int_R	5’ AGGTCGCAGCCAATCATCCA
Gex2	5’ AAGGCCCACGCACAGACTGACAGAATGAAC
IL-10-NMBF-F	5’ GAGATCTCCGAGATGCCTTC
IL-10-NMBF-R	5’ TGTCGGGGTCTTGGTTCTCA
IL-12p40F (bos 1)	5’ TTTGGAGATGCTGGGCAGTACA
IL-12p40R (bos 2)	5’ GATGATGTCCCTGATGAAGAAGC
IDO_F	5’ GGCAAAGGTCATGGAGATGT
IDO_R	5’ CTGCAGTATCCATCACGAAA
RelB_F	5’ ATCACTGCCACCCAGAAGACT
RelB_R	5’ CATGCCAGTGAGCTTCCCGTT
GAPDH_F	5’ ATCACTGCCACCCAGAAGACT
GAPDH_R	5’ CATGCCAGTGAGCTTCCCGTT
PKCβ F	5’ GGGATTATGCAGATGGCCTA
PKCβ R	5’ CCCGGAAGTGGAAGAGTACC

- **Underlined sequence designates binding site for the Restriction enzyme. Primers containing either Sal I or Kpn I word in their name contain restriction site specific for those enzymes. Letters F or R at the end of each primer name stand for Forward and Reverse respectively, and indicate direction of priming on the sequence of interest.**

- **Ovine**

Primer name	*Sequence*
IL-2F (SPIL-2A)	5’ AACTCTTGTCTTGCATT
IL-2R (SPIL-2B)	5’ GATGCTTTGACAAAAGGT
IL-10F (SPIL-10A)	5’ GCAGCTGTACCCAGTTCCCA
IL-10R (SPIL-10B)	5’ AGAAAACGATGACAGCG
IL-12p40F (bos 1)	Same as for human (see above)
IL-12p40R (bos 2)	
IFN- F (SPIFNA)	5’ CCAGATGTAGCTAAGGGTGGGCCTC
IFN- R (SPIFNB)	5’ ATTGATGGCTTTGCGCTG
TNF- F (SPTNFA)	5’ GGCTCTCCTGTCTCCCG
TNF- R (SPTNFB)	5’ GTTGGCTACAACGTGGGCTAC
FoxP3F	5’ CCCACAGTACCCCTTGTCAT
FoxP3R	5’ TTGAGAGAGAAGAGCCCCGT
GAPDH_F	5’ ATCACTGCCACCCAGAAGACT
GAPDH_R	5’ CATGCCAGTGAGCTTCCCGTT

Table 2. Summary of the $MgCl_2$ concentration, primer concentration and resulting product size for the each primer set used in RT-PCR

- **Human**

Primer pair	*Gene amplified (purpose of use)*	*$MgCl_2$ (mM)*	*Primer concentration (μM)*	*PCR product size (bp)*
HLA-G1SalIF HLA-G1KpnIR	HLA-G1 full length (cloning)	1.5	1	1032
HLA-G1SalIF HLA-G5KpnIInt4R	HLA-G5 full length (cloning)	1.0	0.25	974
HLA-G1SalIF HLA-G_int_R	HLA-G1/HLA-G5 (PCR)	1.0	0.25	388
IL-10-NMBF-F IL-10-NMBF-R	IL-10 (PCR)	2.5	1	407
IL-12p40F (bos 1) IL-12p40R (bos 2)	IL-12p40 (PCR)	2.5	0.25	461
IDO_F IDO_R	IDO (PCR)	2.5	1	250
RelB_F RelB_R	RelB (PCR)	2.5	0.5	249
GAPDH_F GAPDH_R	GAPDH (PCR)	2.5	1	152
PKCβ F PKCβ R	PKCβ (PCR)	2.5	0.5	216

- **Ovine**

Primer pair	*Gene amplified (purpose of use)*	*$MgCl_2$ (mM)*	*Primer concentration (μM)*	*PCR product size (bp)*
IL-2F (SPIL-2A) IL-2R (SPIL-2B)	IL-2 (PCR)	2.5	1	409
IL-10F (SPIL-10A) IL-10R (SPIL-10B)	IL-10 (PCR)	2.5	1	309
IL-12p40F (bos 1) IL-12p40R (bos 2)	IL-12p40 (PCR)	2.5	0.25	461
IFN-γF (SPIFNA) IFN-γR (SPIFNB)	IFN-γ (PCR)	2.5	1	278
TNF-αF (SPTNFA) TNF-αR (SPTNFB)	TNF-α (PCR)	2.5	1	338
FoxP3F FoxP3R	FoxP3 (PCR)	1	0.25	217
GAPDH_F GAPDH_R	GAPDH (PCR)	2.5	1	152

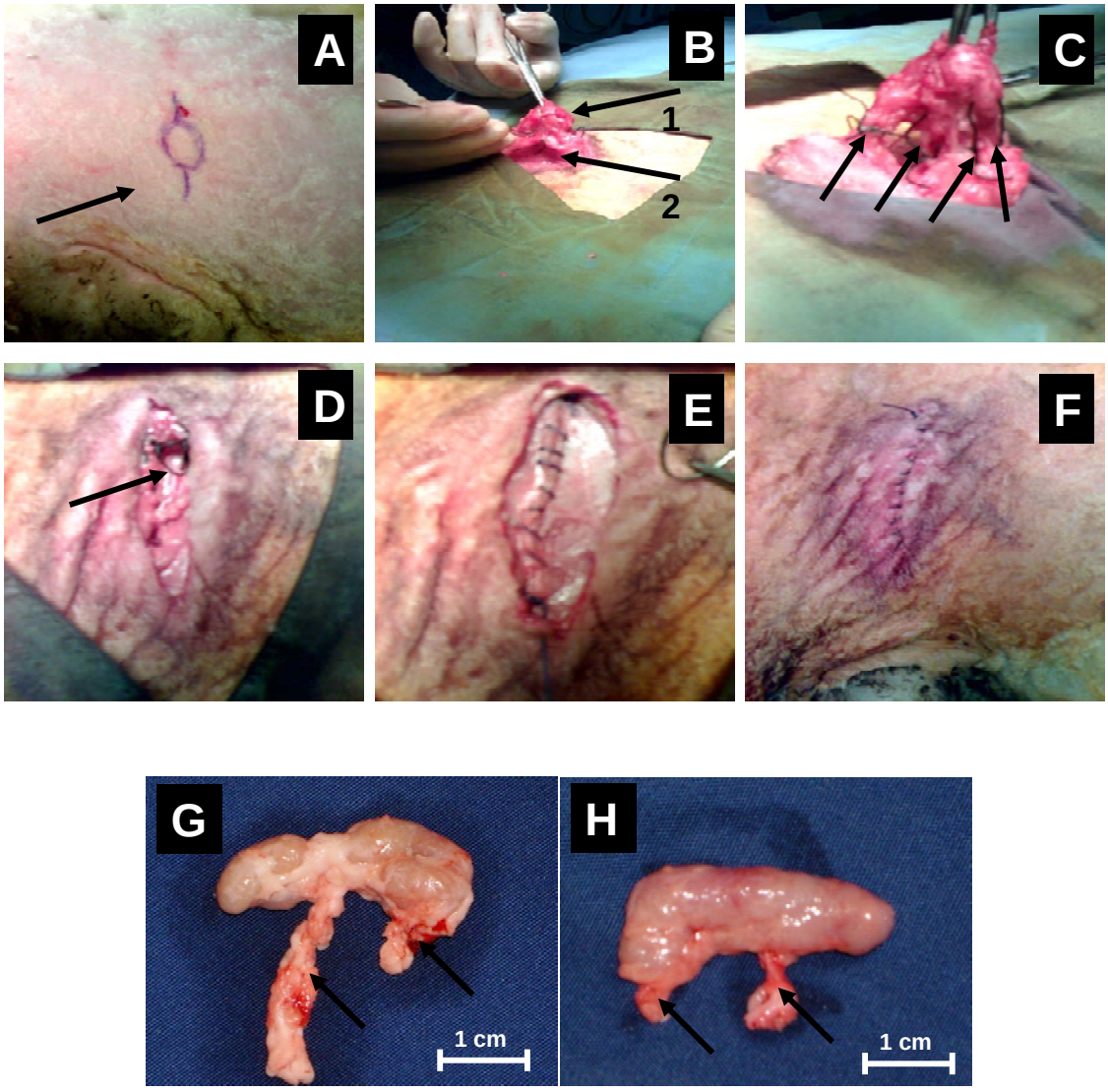
Table 3. Cycling condition summary for each primer pair used in RT-PCR

- **Human**

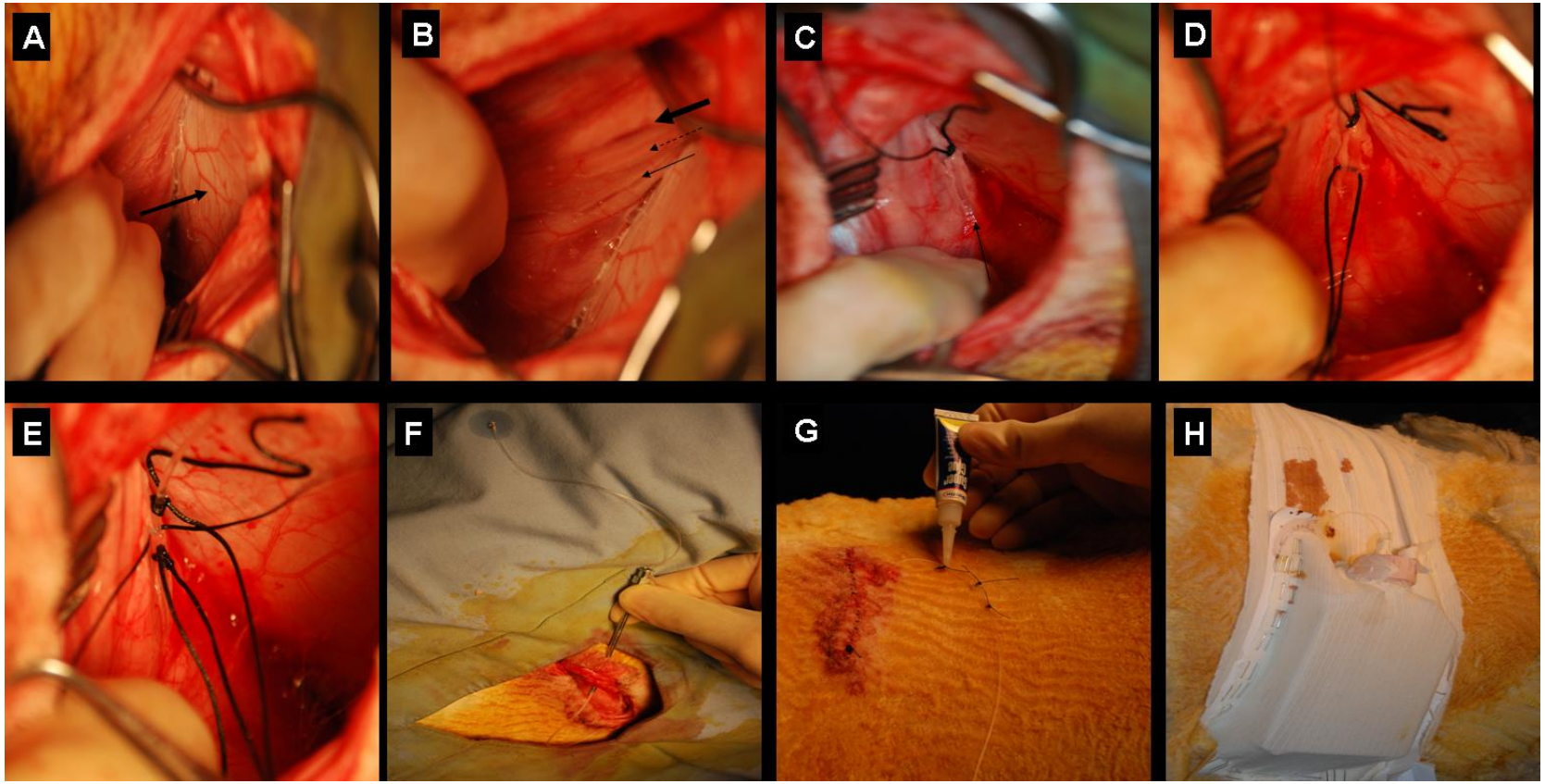
Primer pair	*Denaturing temperature °C / time (sec)*	*Annealing temperature °C / time (sec)*	*Extension temperature °C / time (sec)*
HLA-G1SalIF HLA-G1KpnIR	95/30	60/30	72/30
HLA-G1SalIF HLA-G5KpnIInt4R	95/30	58/30	72/30
HLA-G1SalIF HLA-G_int_R	95/30	58/30	72/30
IL-10-NMBF-F IL-10-NMBF-R	95/30	55/30	72/30
IL-12p40F (bos 1) IL-12p40R (bos 2)	95/30	60/30	72/30
IDO_F IDO_R	95/30	55/30	72/30
RelB_F RelB_R	95/30	55/30	72/30
GAPDH_F GAPDH_R	95/30	55/30	72/30
PKCβ F PKCβ R	95/25	55/25	72/55

- **Ovine**

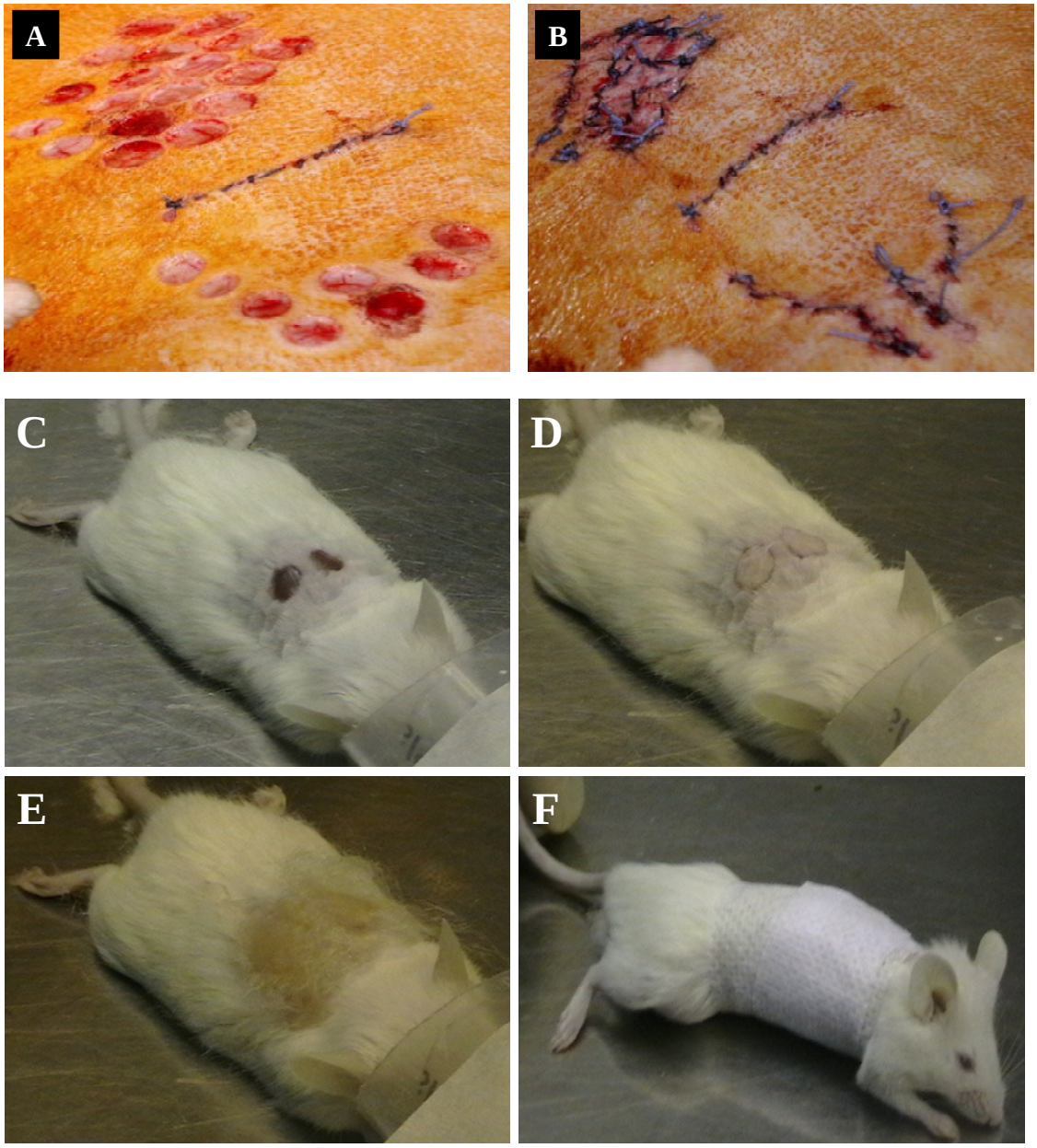
Primer pair	*Denaturing temperature °C / time (sec)*	*Annealing temperature °C / time (sec)*	*Extension temperature °C / time (sec)*
IL-2F (SPIL-2A) IL-2R (SPIL-2B)	94/30	55/30	72/30
IL-10F (SPIL-10A) IL-10R (SPIL-10B)	94/30	55/30	72/30
IL-12p40F (bos 1) IL-12p40R (bos 2)	94/30	55/30	72/30
IFN-γF (SPIFNA) IFN-γR (SPIFNB)	95/45	62/45	72/45
TNF-αF (SPTNFA) TNF-αR (SPTNFB)	95/25	55/25	72/25
FoxP3F FoxP3R	95/45	57/60	72/45
GAPDH_F GAPDH_R	95/30	55/30	72/30



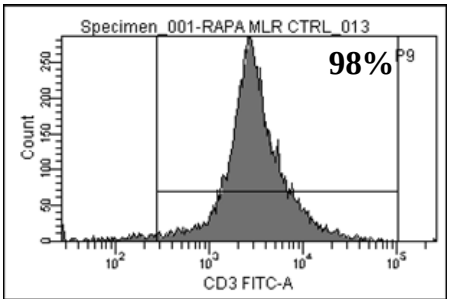
Appendix 4.1 Removal of pre-femoral lymph nodes. (A) Lymph nodes were palpated and the location was marked prior to the incision. (B) Location and the isolation of the lymph node following the incision. (C) Tying off the major blood vessels supplying the lymph none. Arrows indicate position of the major blood vessels. (D) The node was removed by cutting the blood vessels approximately half way between the tie and the node. The arrow indicates the remaining hole where the lymph node used to be. (E) Closure of the fascia using dissolvable sutures and taper needle. (F) Closure of the skin using dissolvable sutures and the reverse cutting needle. (G and H) **Morphology of pre-femoral lymph nodes.** (G) Bi-lobed pre-femoral lymph node. (H) Single-lobed lymph node. Arrows indicate major blood vessels supplying the lymph nodes.



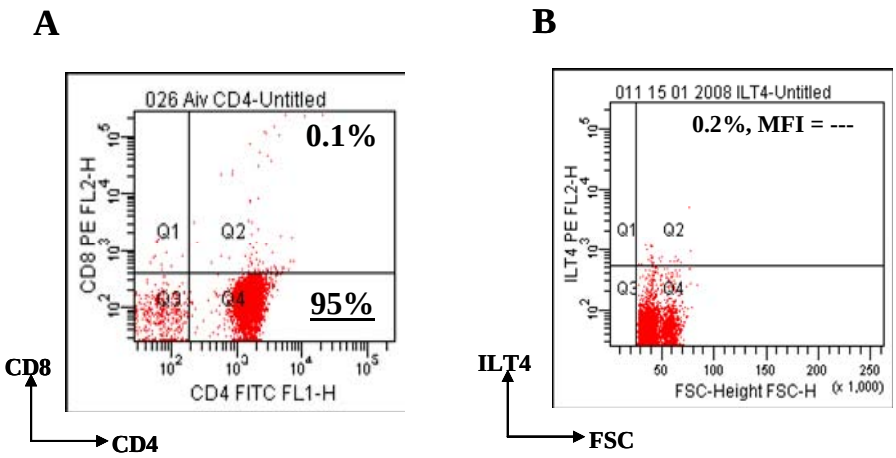
Appendix 4.2 Outline of the cannulation procedure. (A) Following the incision, fat and fascia were gently separated to a depth of approximately 5 cm, reaching the abdominal wall (see arrow) (B) Initial visualization of the pseudo-efferent lymphatic vessel. Thin black arrow indicates lymphatic vessel, while dashed and thick black line depict nerve or blood vessel respectively (C) At the most dorsal end of the lymphatic vessel a tie was placed in order to enhance visualization of the vessel. Arrow indicates swelling of the vessels. (D) Placing of the additional suture underneath of the swollen lymphatic vessel, in order to secure the inserted cannula in place. (E) Small incision was made on the lymphatic vessel through which the cannula has been inserted. The cannula was secured in place with 2-3 sutures (F) The cannula was guided out through the skin via hollow needle, which was used to puncture the skin and fascia. (G) Following the skin closure cannula was secured onto the skin with approximately 3 sutures and glue to restrict the movement of the cannula. (H) Cannula was placed into the collection bottle containing heparin and gentamicin, and then secured into the pouch.



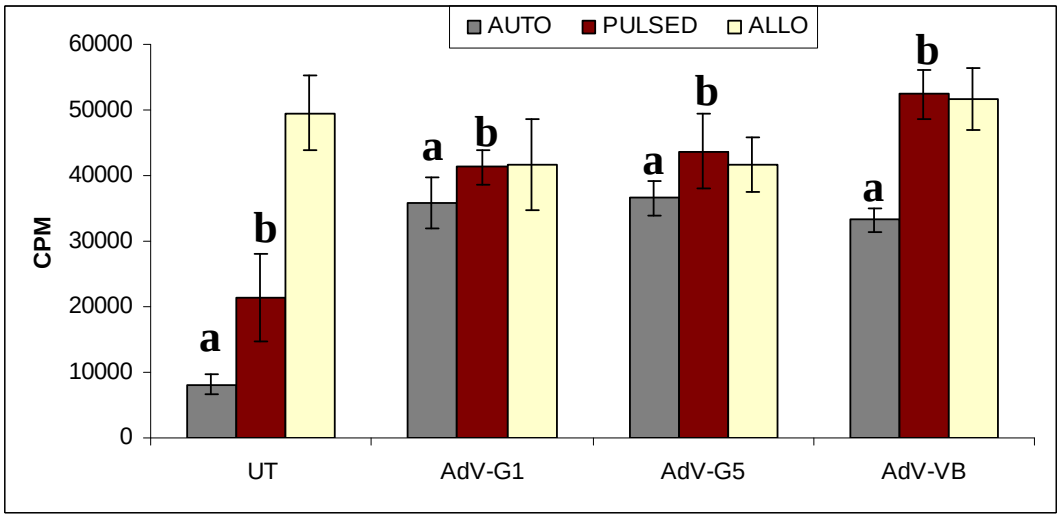
Appendix 4.3. Image of skin removal from sheep and NOD/SCID skin transplantation. (A) 8mm punch skin biopsy was excised from the non-wool bearing region (B) skin was sutured using 1.0 Vicryl absorbable sutures. Surgical site was covered with antibiotic cream and allowed to heal. Animals also received intra muscular antibiotic as a prophylactic treatment against infection. (C) Approximately 8mm incision was made to accommodate for the skin graft (D) Positioning of the skin grafts over the incision (E) Application of calcium alginate to the wound (F) Bandaging of the mice



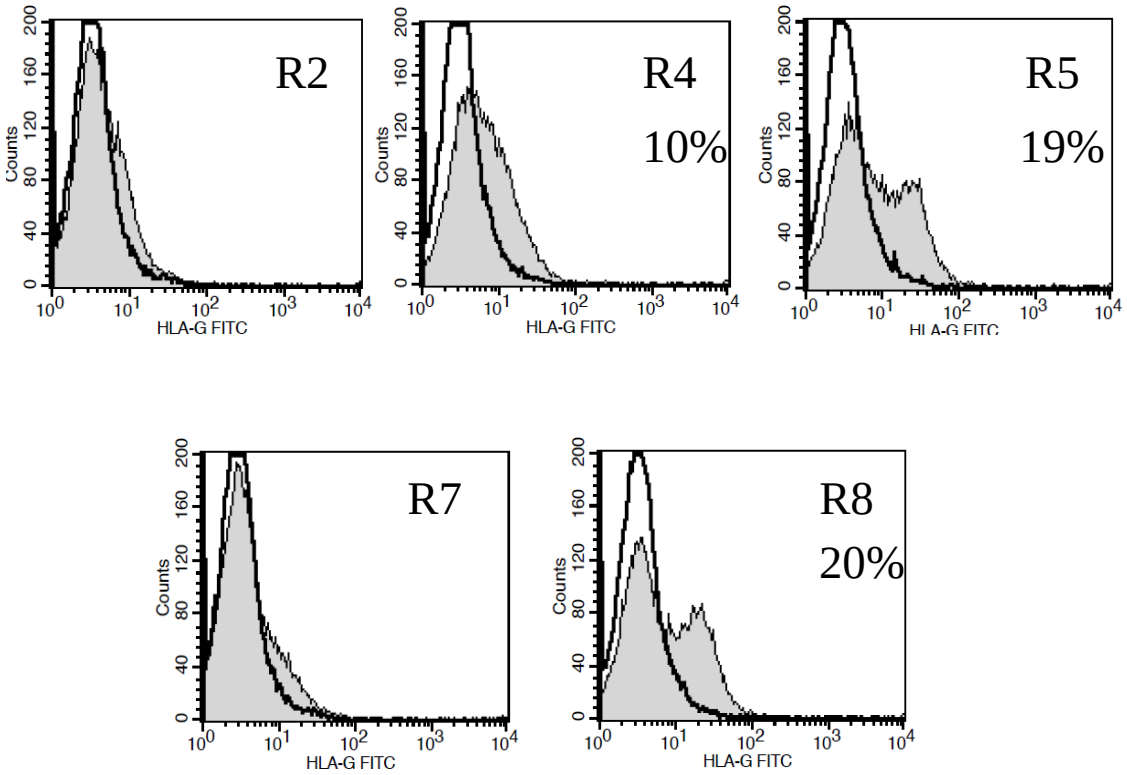
Appendix 6.1. Purity of T cells following CD3 isolation. Transfected DC were co-cultured with allogeneic T cells in 1:10 (DC:T cell) ratio for 5 days. At day 5 cells were collected and positively selected using anti-CD3 microbeads. Positive fraction was then subjected to flowcytometric analysis using anti-CD3 mAb. The histogram shows the percentage positive $CD3^+$ T cells obtained post microbeads isolation. The data are representative of at least 3 independent experiments.



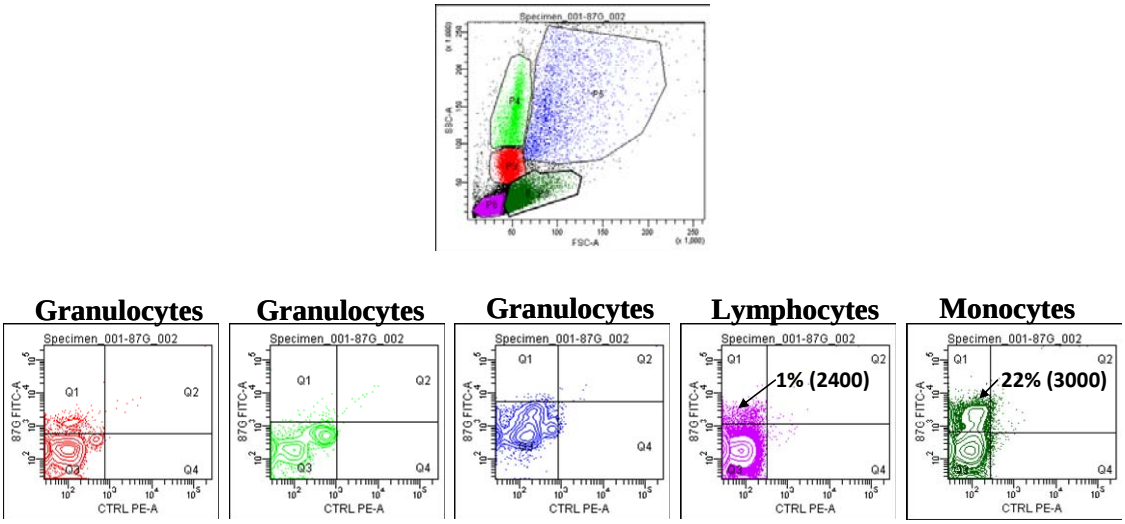
Appendix 6.2. Expression of CD8 and ILT4 on $CD4^+$ T cells used in trogocytosis. $CD4^+$ T cells were negatively selected using T_{REG} isolation kit from Miltenyi. This kit depleted $CD4^+$ T cell population of $CD8^+$ T cells, $CD19^+$ B cells, $CD14^+$ monocytes, $CD16^+$ macrophages, $CD56^+$ NK cells, $CD123^+$ platelets and $CD235a^+$ red blood cells. (A) Percentage of CD8 cells in CD4 T cell fraction is recorded in top right corner while percentage of CD4 T cells is recorded in the bottom right corner (B) $CD4^+$ T cell population purified using T_{REG} kit above was labelled with anti-ILT4 mAb (42D1). The percentage of ILT4 expressing CD4 T cells is recorded in the top right corner. The data are representative of at least 3 independent experiments.



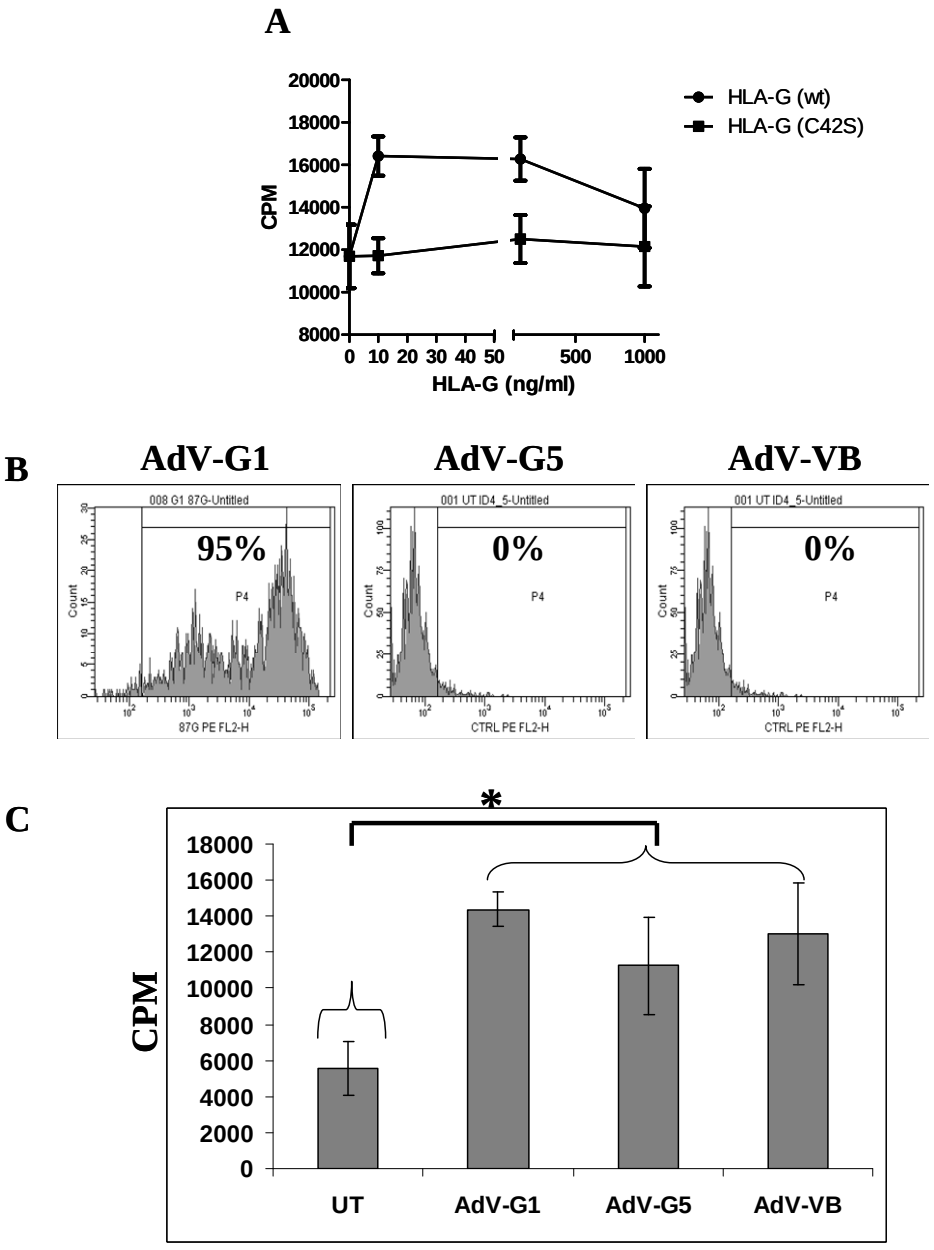
Appendix 6.3. Adenoviral vectors mount an immune response during autologous MLR. For transfection experiment DC were either left untreated or transfected with AdV-HLA-G1, AdV-HLA-G5 and AdV-VB (100 MOI) for 48h. DC were then washed 3 times in PBS and plated at concentration of $1x10^4$/well. For pulsing experiments (indirect allorecognition pathway) DC ($1x10^6$) were transfected for 24h before 1ml of cell lysates from $1x10^7$ PBMC was added to DC for additional 24h. DC were then washed 3 times in PBS and plated as above. DC were then challenged with either autologous or allogeneic T cells ($1x10^5$/well). [^{3}H]-thymidine incorporation was measured after 5 days of co-culture and recorded as mean CPM (+/- SD). Data are representative of two independent experiments. a = (p=0.02) and b = (p=0.03) annotate significance for transfected autologous and antigen pulsed group, respectively, when compared to the untreated group.



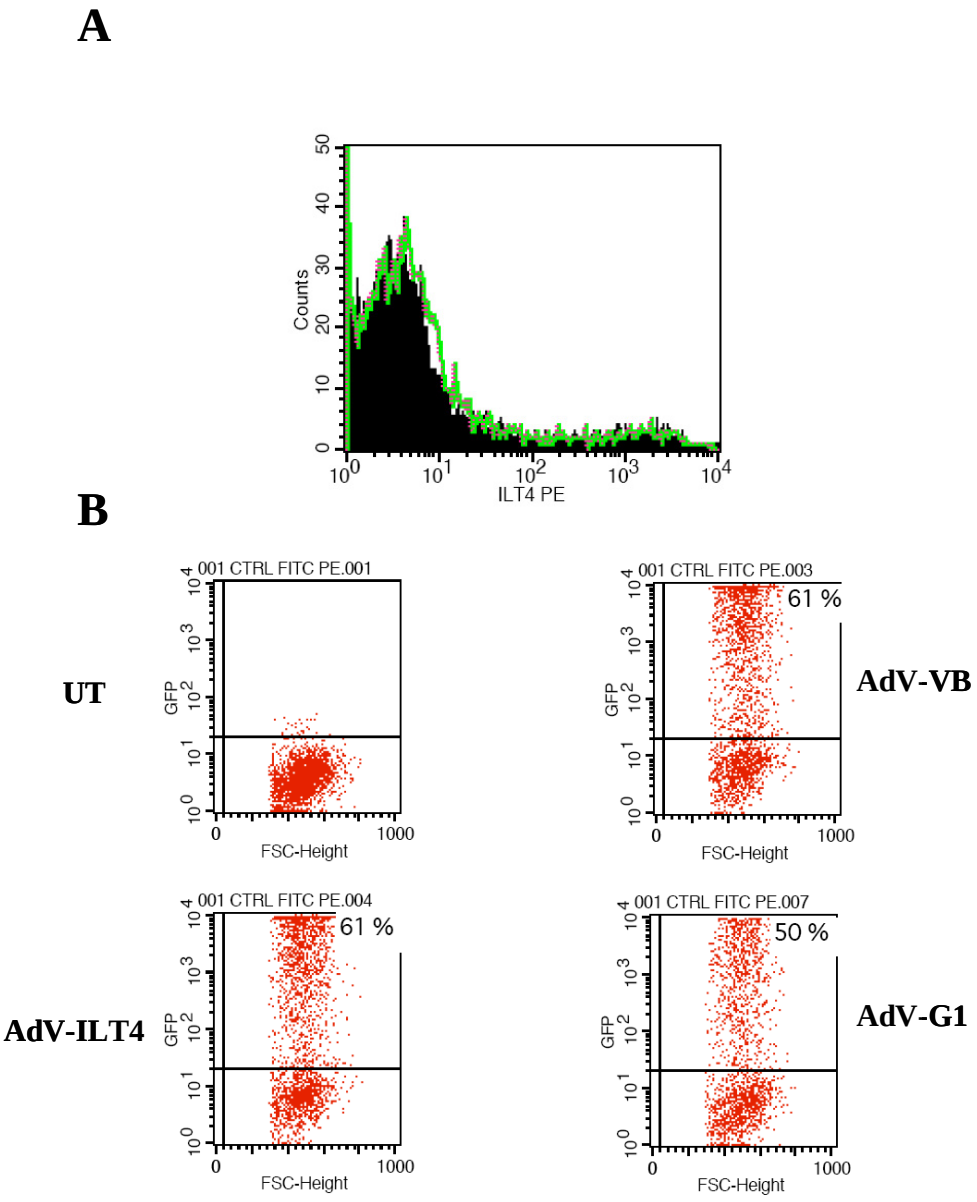
Appendix 6.4. Cross-reactivity of anti-HLA-G (87G) with sheep PBMC. Ovine PBMC were purified from five random animals using Ficoll gradient separation and labelled with anti-human HLA-G (Clone 87G) for 30 min on ice. 87G was detected using secondary FITC-conjugated anti-mouse mAb. Results are reported as histograms and the percentage of 87G expressing cell is shown only in positive samples.



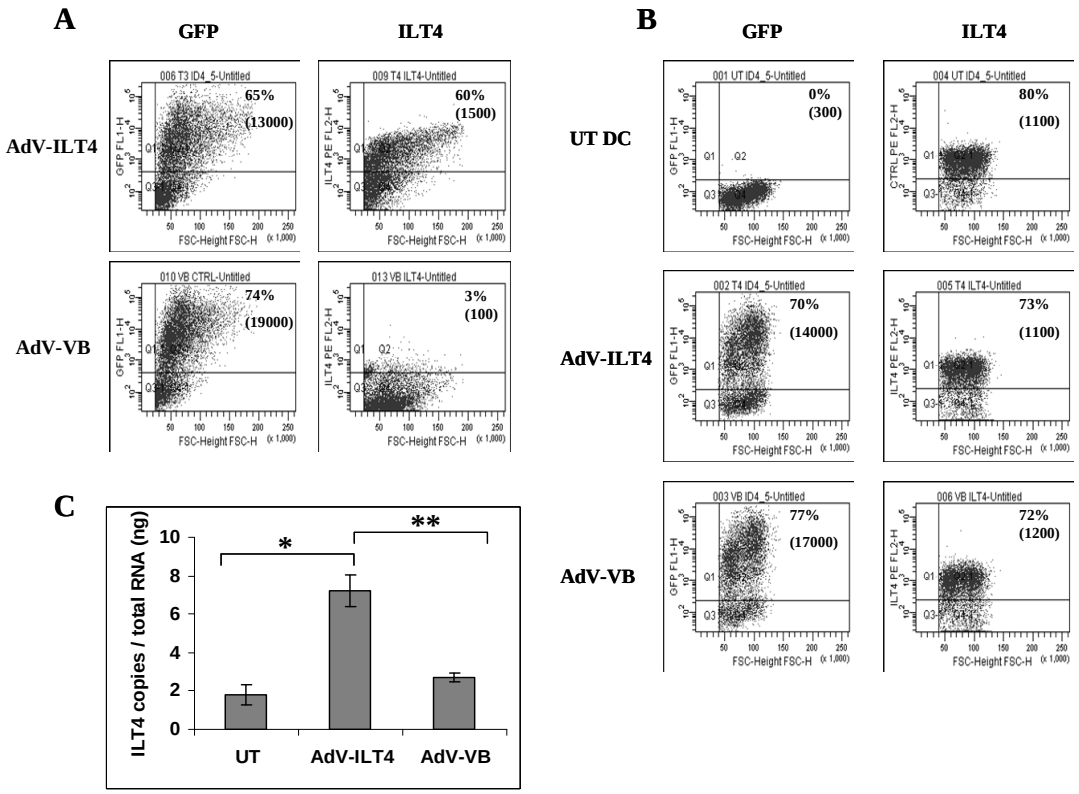
Appendix 6.5. Analysis of sheep cell subsets cross-reacting with of anti-human HLA-G (87G). Ovine PBMC were purified from five random animals using Ficoll gradient separation and labelled with anti-human HLA-G mAb (Clone 87G) for 30 min on ice. 87G was detected using secondary FITC anti-mouse mAb. Different cell populations were gated based on their size and complexity using forwards and side scatter, respectively. Specific 87G staining was represented as density plots, where percentage of 87G expressing cells and MFI (parenthesis) are also reported.



Appendix 6.6. The effect of human HLA-G on alloimmune responses in sheep. (A) Freshly isolated lymphatic DC were used as stimulator cell in DC-MLR assay against PBMC. Purified human HLA-G (wt and C42S) was added at 10, 100 and 1000 ng/ml, at the beginning of DC-MLR. ^{3}H-thymidine incorporation was measured after 5 days of co-culture and recorded as mean CPM (+/- SD). Data are representative of two independent experiments (B) DC were either left untreated or transfected with AdV-HLA-G1, AdV-HLA-G5 and AdV-VB (100 MOI) for 48h. Surface expression of human HLA-G in ovine DC was determined using anti-human HLA-G mAb (87G) (C) Transfected DC were then washed 3 times in PBS and plated at concentration of $1x10^{4}$/well. DC were then challenged with autologous PBMC ($1x10^{5}$/well).^{3}H-thymidine incorporation was measured after 5 days of co-culture and recorded as mean CPM (+/- SD). Data are representative of two independent experiments (*P = 0.02).



Appendix 6.7 Ovine DC transfected with Adenoviral vectors containing ILT4 cDNA do not express surface ILT4 . Freshly isolated lymphatic DC were transfected with AdV-HLA-G1, AdV-ILT4 and AdV-VB (100 MOI) for 48h. (A) Flowcytometric analysis of ILT4 expression in ovine DC following Adenoviral transfection was determined using anti-human ILT4 mAb (42D1). Black = Isotype control, Green = AdV-ILT4 and Red = AdV-VB (B) Transfected DC were analysed for expression of GFP and the percentage of GFP positive cells is indicated in each dot plot. Data are representative of one experiment



Appendix 6.8 Human DC transfected with Adenoviral vectors containing ILT4 cDNA do not express surface ILT4 . Fresh monocyte-derived DC or HEK 293 cells were transfected with AdV-ILT4 and AdV-VB (100 MOI) for 48h. (A) Flowcytometric analysis of ILT4 surface expression in HEK 293 cells. Percentage of $ILT4^+$ cells together with MFI (parenthesis) is indicated on each dot plot. (B) Flowcytometric analysis of ILT4 surface expression in fresh DC. Percentage of $ILT4^+$ cells together with MFI (parenthesis) is indicated on each dot plot (C) PCR analysis of ILT4 mRNA expression in transfected DC. Data are representative of three independent experiment (* $p < 0.03$), (** $p < 0.02$).

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