Supplemental Figure Legends:

Fig. S1: Low-dose C57BL/6 donor spleen cells induced autoantibody production and tissue collagen deposition. Lethally irradiated BALB/c recipients were transplanted with C57BL/6 spleen cells ($1.25x10^6$). **A:** 15 and 60 days after HCT, recipient serum samples were tested for presence of autoantibodies by staining recipient-type Rag-$2^{-/-}$ BALB/c skin and salivary gland tissues. Representative photomicrographs of GVHD recipient serum autoantibody staining of Rag-$2^{-/-}$ skin and salivary gland tissues are shown. Autoantibody staining is shown in green. One representative result is shown from 8 samples evaluated in each group. **B:** 60 days after HCT, skin tissues from GVHD recipients given C57BL/6 donor spleen cells and GVHD-free control TBCD-BM recipients were stained with trichrome for collagen (blue). A representative photomicrograph is shown from 1 of 6 recipients in each group.

Fig. S2: Induction of cGVHD in C57BL/6.SJL recipients by transplantation of MHC-matched C3H.SW splenic $CD8^+$ T and TBCD-BM cells. C57BL/6.SJL recipients were exposed to 1100 cGy TBI and transplanted with $CD4^+$ and $CD44^+$ cell-depleted naïve $CD8^+$ T cell-enriched splenocytes (~ 2 x 10^6 $CD8^+$ T cells). Recipients were monitored for bodyweight change, diarrhea, hair-loss, and survival. At 15 and 60 days after HCT, serum autoantibody was measured by staining recipient-type Rag-$2^{-/-}$ C57BL/6 skin and salivary gland tissues. 60 days after HCT, the percentage of $CD4^+CD8^+$ thymocytes and histopathology of colon, jejunum, skin, and salivary gland was evaluated. Recipients showed no signs of diarrhea (data not shown). **A-C**: Percentage of bodyweight changes, hair-loss, and survival. Data are combined from a total of 8 recipients in 2 replicate experiments. **D**. Serum autoantibody staining of Rag-$2^{-/-}$ C57BL/6 skin and salivary gland tissues. DAPI staining is shown in blue, and autoantibody staining is shown in green. A representative photo is shown from 1 of 6 recipients in each group. **E**. A

representative flow cytometry pattern of $CD4^+CD8^+$ thymocytes is shown from 1 of 6 recipients in each group. **F.** A representative photomicrograph is shown from 1 of 6 recipients in each group. Arrows indicate: blunting crypts in the colon; loss and blunting of crypts in the jejunum; expansion of dermis and loss of hair-follicles and fat tissues in the dermis; infiltration and destruction of secretory follicles in the salivary gland.

Fig S3: Comparison of de novo-generated donor $CD4^+$ and $CD8^+$ T cells in mediating cGVHD (supplement for Fig. 6B). Lethally irradiated BALB/c recipients were transplanted with donor $CD8^+$ T cells (0.5×10^6) with TBCD-BM cells (2.5×10^6) from $CD4^+$ T cell- or $CD8^+$ T cell-deficient C57BL/6 donors. A representative result is shown from 1 of 6 recipients in each group. **A.** A representative flow cytometry pattern of de novo-generated T cells in the recipients given $CD4^+$ T cell-deficient or $CD8^+$ T cell-deficient BM cells. **B.** A representative photo of recipients given donor $CD8^+$ T cells and $CD4^+$ T cell-deficient or $CD8^+$ T cell-deficient BM cells. **C.** Serum autoantibody staining of Rag-$2^{-/-}$ skin and salivary gland tissues. **D.** Histopathology of skin and salivary gland tissues of recipients given donor $CD8^+$ T cells and $CD4^+$ T cell-deficient or $CD8^+$ T cell-deficient BM cells. Arrows indicate: expansion of dermis and loss of fat in the skin as well as infiltration and destruction of salivary gland secretory follicle.

Fig. S4: Comparison of anti-CD4 and rat IgG in preventing cGVHD (supplement for Fig. 6C). Lethally irradiated recipients were transplanted with donor $CD8^+$ T cells (0.5×10^6) and TBCD-BM cells from wild-type C57BL/6 donors. On 15 and 30 days after HCT, recipients were injected with anti-CD4 mAb or control rat IgG (500μg/mouse). Data were combined from a total of 8 recipients in each group from two replicate experiments. **A.** $CD4^+$ T depletion and recovery

after anti-CD4 mAb treatment (N=8). **B.** A representative photo of recipients treated with anti-CD4 or control rat-IgG. **C.** Serum autoantibody staining of Rag-2$^{-/-}$ skin and salivary gland tissues (N=6). **D.** Representative photomicrograph of histopathology (N=6). Arrows indicate expansion of dermis and loss of fat in the skin, and infiltration and destruction of salivary gland secretory follicles. **E.** Percentage and yield of $CD4^{+}CD8^{+}$ thymocytes in recipients treated with anti-CD4 mAb or rat IgG (N=6).

Supplemental Figures:

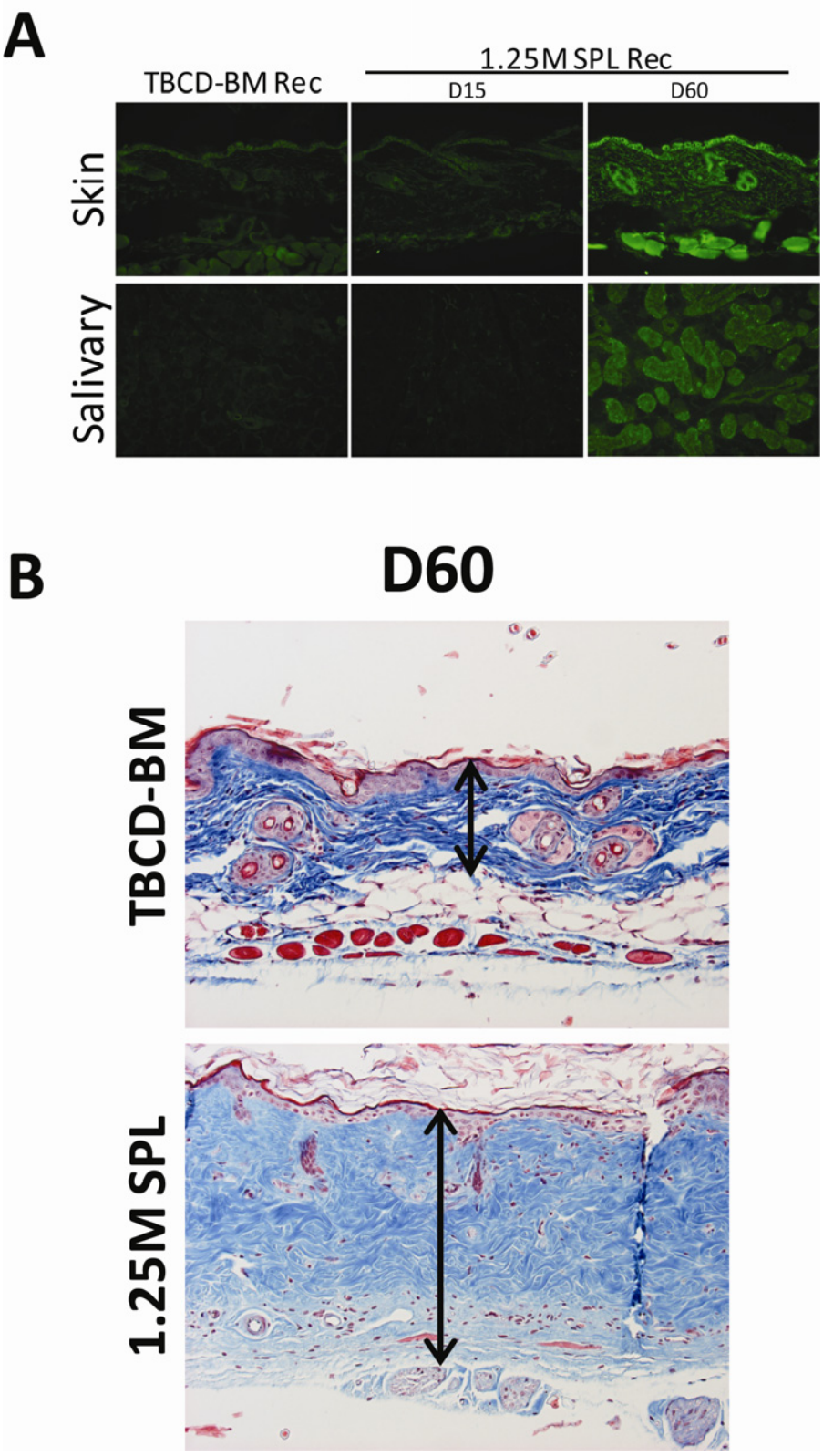
A
TBCD-BM Rec
1.25M SPL Rec
D15
D60
Skin
Salivary
B
D60
TBCD-BM
1.25M SPL

Fig. S1

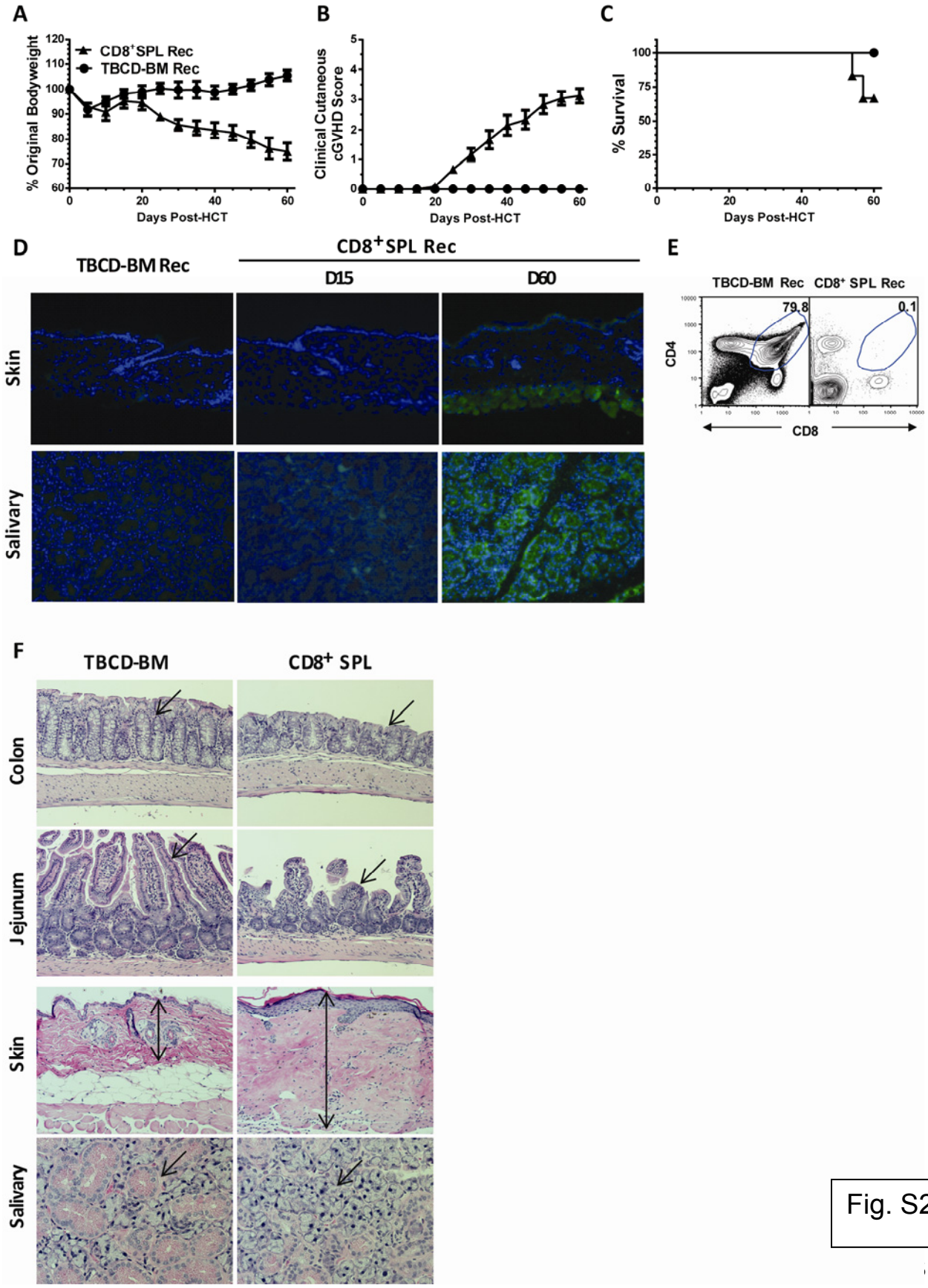
A
% Original Bodyweight
CD8+SPL Rec
TBCD-BM Rec
Days Post-HCT
B
Clinical Cutaneous cGVHD Score
Days Post-HCT
C
% Survival
Days Post-HCT
D
TBCD-BM Rec
CD8+SPL Rec
D15
D60
Skin
Salivary
E
TBCD-BM Rec
CD8+ SPL Rec
79.8
0.1
CD4
CD8
F
TBCD-BM
CD8+ SPL
Colon
Jejunum
Skin
Salivary

Fig. S2

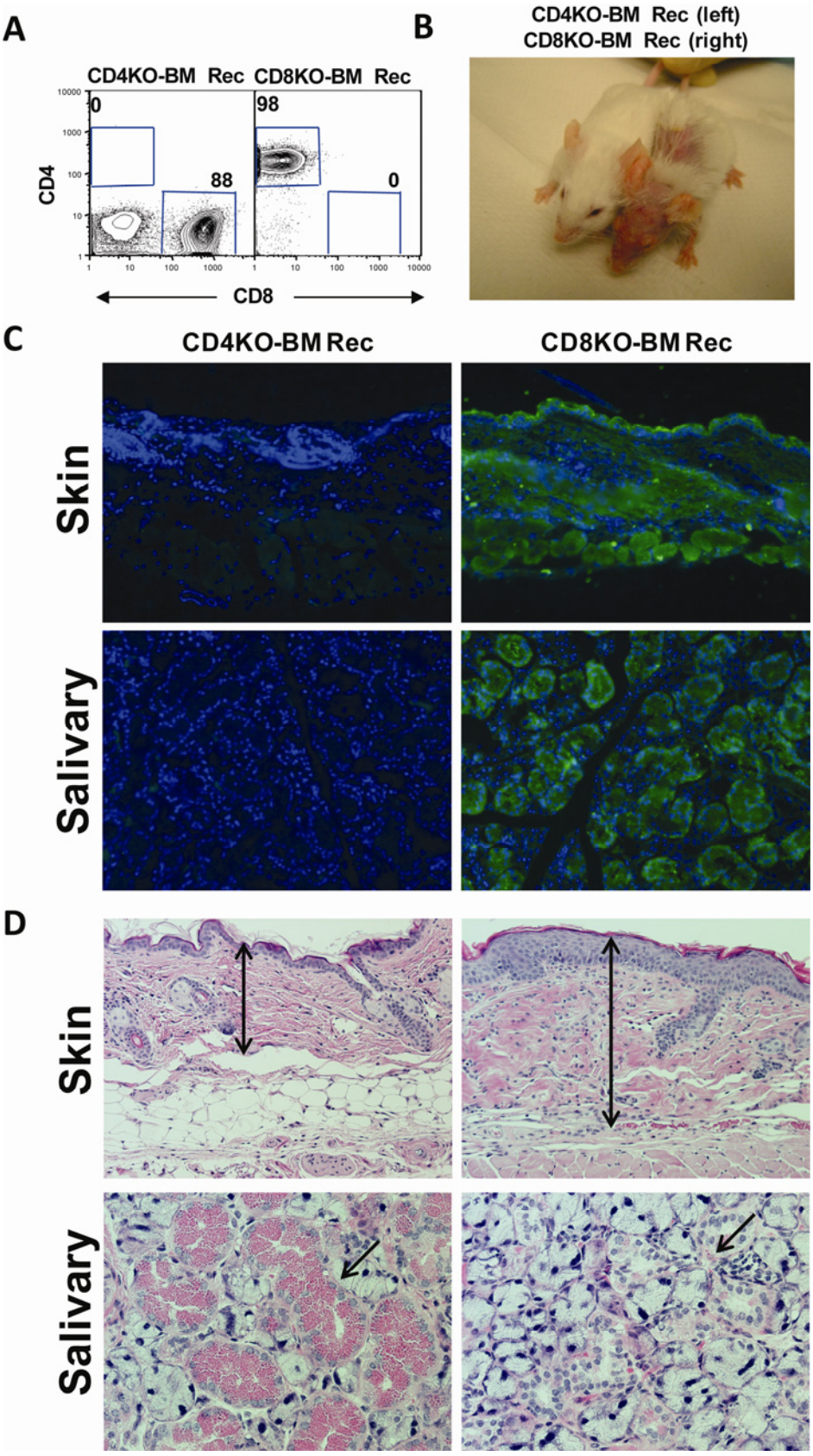
A
CD4KO-BM Rec
CD8KO-BM Rec
0
98
88
0
CD4
CD8
B
CD4KO-BM Rec (left)
CD8KO-BM Rec (right)
C
CD4KO-BM Rec
CD8KO-BM Rec
Skin
Salivary
D
Skin
Salivary

Fig. S3

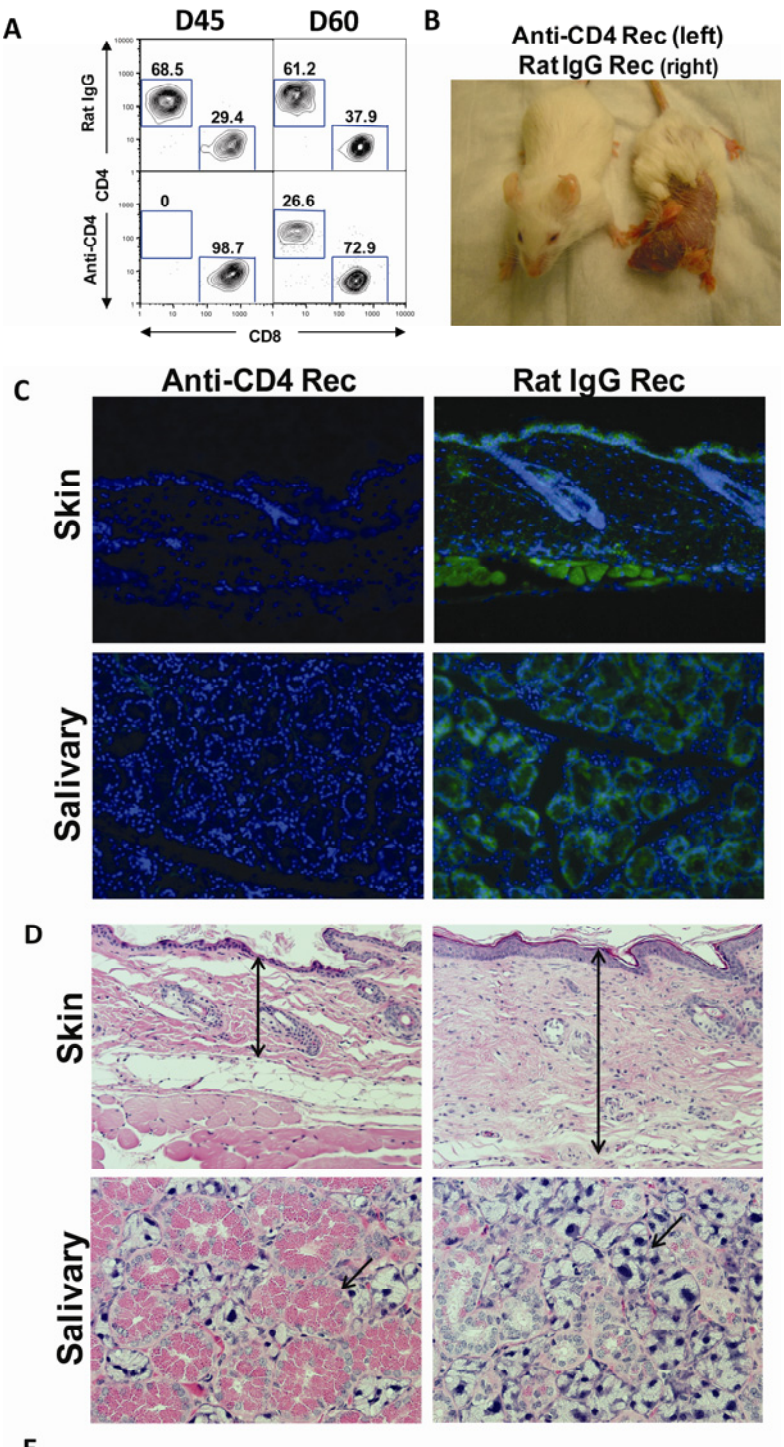
A
D45
D60
Rat IgG
CD4
Anti-CD4
CD8
68.5
29.4
61.2
37.9
0
98.7
26.6
72.9
B
Anti-CD4 Rec (left)
Rat IgG Rec (right)
C
Anti-CD4 Rec
Rat IgG Rec
Skin
Salivary
D
Skin
Salivary
E
Anti-CD4 Rec
Rat IgG Rec
% CD4+CD8+
Yield of CD4+CD8+ (X10^7)

Fig. S4