Figure Legends

Supplementary Figure 1

(A) Immunoblot analysis of IL-15 in normal donor CD4+ T-cells, SS patient CD4+ T-cells and patient derived cell lines. Protein lysates were probed for expression of IL-15; β-Actin was used as housekeeping control. (**B**) Overall genomic region and specific CpG dinucleotide locations within CpG island of IL-15 promoter used for pyrosequencing analysis. (**C**) Schematics of mutation or deletion of putative Zeb1 binding site in IL-15 promoter. (**D**) Semi-quantitative SYBR ChIP PCR analysis for binding of Zeb1 to the IL-15 promoter in CTCL patients and normal donor CD4+ cells. Input DNA from each normal donor and CTCL patient was used as control; data presented as mean ± SEM, N=3 for CTCL patients and normal donors. **(E)** Immunoblot analysis of ZEB1 in normal donor CD4+ T-cells, SS patient CD4+ T-cells and patient derived cell lines. Protein lysates were probed for expression of IL-15; β-Actin was used as housekeeping control. (**F**) Relative expression of ZEB1 protein in normal donor CD4+ T-cells, SS patient CD4+ T-cells and patient derived cell lines measured by densitometry analysis of immunoblots in supplementary figure 1E. (**G**) Percentage increase in *IL-15* transcript in normal donor CD4+ T-cells transfected with sh-Zeb1 plasmids (clone 1-4), relative to normal donor CD4+ T-cells transfected with sh-control plasmid. *IL-15* transcript was normalized to *18S* and the values for normal donor CD4+ T-cells transfected with sh-control plasmid (N=1). For each panel, data are presented as mean ± SEM, *P ≤ 0.05, **P ≤ 0.01, ****P ≤ 0.0001 unpaired or paired two-tailed student's t-test.

Supplementary Figure 2

(**A**) Representative flow cytometric histogram is shown for CD3 expression in mononuclear cells from skin of WT and IL-15 tg mice. (**B**) Absolute number of CD3+ T-cells in total mononuclear cell isolated from skin of WT and IL-15 tg mice. Data presented as mean ± SEM, n=8 for WT mice and n=14 for IL-15 tg mice. (**C**) WT and IL-15 tg skin sections were stained for expression of CLA (red, upper row) and CCR4 (red, lower row); cells were counterstained for nuclei with DAPI (blue). Representative images of immunoflorescence analysis showed abundant expression of CLA and CCR4 in IL-15 tg skin (right column); consistent with a skin-specific homing pattern as seen in patients. Red florescence seen in WT skin is from auto-florescence of hair follicles. Scale bar = 100μM. (**D**) Quantification of CD4+CD44^{hi} cells while gating on CD3+ cells from skin of WT and IL-15 tg mice. Data presented as mean ± SEM, N=8 for WT mice and N=14 for IL-15 tg mice. (**E**) The quantification of CD4+CD62L- cells in CD3+ mononuclear cells shows a significantly increased frequency of CD4+CD62L- cells in skin from IL-15 tg compared to WT mice. Data presented as mean ± SEM, n=8 for WT mice and n=14 for IL-15 tg mice. (**F**) CD3+CD4+ mononuclear cells isolated from skin were assessed for TCRVβ expression by FACS analysis. Representative picture of flow cytometric histogram showed oligoclonal CD3+CD4+ cells as shown by florescence on the x-axis. (**G**) Quantification of expression of CD26+ cells from skin of WT and IL-15 tg mice. Data presented as mean ± SEM, N=3 each. (**H**) Immunoblot analysis of PLS3, GATA3 and CD164

in WT and IL-15 tg (TG) skin lysates. Protein lysates were probed for expression of PLS3, GATA3 and CD164; Actin was used as housekeeping control. (**I**) Immunohistological analysis of skin from transplanted mouse for CD8 antigen. (**J**) FACS analysis of second transplant mouse malignant cells for surface expression of IL-15Rα. (**K**) MTS cell assay to analyze effects of inhibiting JAK1/3 pathway in malignant cells from the second transplant mouse with Tofacitinib for 48 hours. As seen here, inhibition of JAK1/3 pathway in the malignant cells induced cell death in cell culture. Cell viability as determined by the MTT assay of malignant cells treated with 1uM Tofacitinib versus vehicle control.

Supplementary Figure 3

(A) Immunoblot analysis of HDAC1 in normal donor CD4+ T-cells, SS patient CD4+ T-cells and patient derived cell line, Hut78. Protein lysates were probed for expression of HDAC1; β-Actin was used as housekeeping control. (**B**) Relative expression of HDAC1 protein in normal donor CD4+ T-cells, SS patient CD4+ T-cells and Hut78 cell line measured by densitometry analysis of immunoblots in supplementary figure 3A. (**C-D**) Low and high magnification of confocal immunofluorescence analysis of normal donor CD4+ T-cells incubated chronically with IL-15 for 30 days were compared to day 0 cells from the same donor for expression of HDAC1, and HDAC6 (each stained with green fluorescence). Cells were counterstained for nucleus using DAPI (blue). (**E**) Analysis of CD4+ T-cell proliferation in presence of IL-15. Approximately 1 x 10^6 normal donors CD4+ T-cells were incubated with 100ng/ml of IL-15 in 30-day

culture. Cells were counted by trypan blue exclusion method and replenished with fresh medium containing IL-15 every 72 hours (mean ± SEM, N=3 each).

Supplementary Figure 4

(**A**) Immunoblot analysis for expression of p21 protein in normal donor CD4+ cells following ten days of incubation in IL-15 compared to unstimulated normal donor CD4+ T-cells. Actin was probed in same blot as housekeeping control. (**B**) Freshly harvested normal donor CD4+ T-cells were transfected with either GFP-control plasmid or GFP-shRNA plasmid for HDAC1 or HDAC6 by electroporation. Cells were incubated for 12 hours in culture and sorted for GFP expression. Approximately, 2 x 10^5 cells/well were used for trans-well migration assay. GFP+ cells that migrated towards IL-15 gradient were counted after 12 hours. Data is presented as percent migration of cells (mean ± SEM, N=3 for each condition).

Supplementary Figure 5

(A) Pie chart showing the distribution of HDAC1 occupancy in normal donor CD4+ T-cells (upper left) compared to patient CD4+ T-cells (upper right) and normal donor CD4+ T-cells stimulated with 100ng/ml IL-15 for 24 hours (lower left). **(B)** Meta-gene representation of global occupancy status of HDAC1 and H3K27Ac at active and promoter regions centered on a +/- 5 kb window around reference. For super-enhancers the x-axis shows the start and end region flanked by +/- 5kb of genomic sequence. **(C)** Venn diagram showing the overlapping genes (for HDAC1 and H3k27Ac occupancy) in normal donor CD4+

T-cells (red), CTCL patient CD4+ T-cells (blue) and normal donor CD4+ T-cells stimulated with 100ng/ml IL-15 for 24 hours (green). **(D)** Classification enrichment was determined using the Ingenuity Pathway Analysis of upregulated HDAC1 occupied genes for enriched GO biological process in normal donor CD4+ T-cells (red), CTCL patient CD4+ T-cells (blue) and normal donor CD4+ T-cells stimulated with 100ng/ml IL-15 for 24 hours (green). **(E)** HDAC1 binding across enhancers of miR-21 genes in normal donor CD4+ T-cells, CTCL patient CD4+ T-cells and normal donor CD4+ T-cells stimulated with 100ng/ml IL-15 for 24 hours. **(F)** Relative expression of miR-21 in normal donor and circulating CD4+ cells from MF patient. Mature miR-21 transcript was normalized to RNU43 and the values are presented as mean ± SEM, N=3 each. (**G**) Relative expression of miR-21 in skin and peripheral blood CD4+ cells from WT and IL-15 tg (TG) mice. Samples were evaluated for expression of mature miR-21 transcript and normalized to *U6.* The values are presented as mean ± SEM, N=3 for each condition.

Supplementary Figure 6

(**A**) High magnification and (**B**) low magnification histological analysis of IL-15 Tg skin. Cutaneous lymphoma, although not clinically apparent, was confirmed histologically in 4-weeks old IL-15 tg mice. Representative microphotographs of hematoxylin and eosin (H&E) staining of skin sections showed presence of atypical lymphocytic infiltrate. Small lymphocytes are also distributed among the keratinocytes in the epidermis and hair follicle epithelium. (**C**) High and (**D**) low

magnification immunohistochemical analysis of skin for CD3 antigen in 4-weeks old IL-15 tg mouse.

Supplementary Figure 7

The CTCL mouse disease severity scoring system is on a 0 to 100 scale, with 100 being the highest (most severe) score.