Having confirmed that TM-β1 antibody is effective in the efficient blockade of IL-15 activity, we administered TM-β1 antibody as a bolus of 200 micrograms intraperitoneally twice a week, 3 days apart for a period of 8 weeks to a group of three $T3^b$-hIL-15 Tg mice that were 6 months of age at the beginning of the experiment. Our selection of the dosage and frequency of antibody administration was guided by previously reported similar studies. Two other control groups were included to provide base line cellular, gross pathological and histopathological data for comparison with the antibody treated group and comprised of age matched non-transgenic litter-mates (n=3) and $T3^b$-hIL-15 Tg mice with no antibody therapy (n=3).

TM-β1 antibody administration reverses abnormal peripheral blood cell profiles. In $T3^b$-hIL-15 Tg mice the expression of human IL-15 is exclusively limited to the intestines of these animals (16). However, the sera of these animals contain measurable levels of circulating human IL-15 in the range of 50-100 picograms per ml as measured by ELISA which is likely to reflect the seepage of enterocyte-synthesized IL-15 into the circulation of these animals (16). When we performed a complete blood count (CBC) on peripheral blood samples of these $T3^b$-hIL-15 Tg mice (see Table 1), there was consistent evidence of leukocytosis with total white blood cell counts being approximately 3 to 5-fold higher than those seen in the non-transgenic litter-mates. However, no meaningful differences in the red blood cells or platelet counts were noted in the transgenic animals despite their extensive leukocytosis thus likely reflecting the absence of any generalized bone marrow disfunction in these animals. We attribute the expansion of peripheral blood lymphocytes to increased levels of circulating IL-15 in these animals in a manner similar to what one would see in mice with repeated exogenous IL-15 administrations that leads to the expansion of peripheral blood lymphocytes. With repeated TM-β1 administration, we noted a progressive decline in the total white blood cell counts in blood samples collected longitudinally from

animals during the course of antibody treatment (see Table 1), thus providing a way to monitor the effectiveness of TM-β1 antibody treatment. Having confirmed a measurable impact on total white blood cell counts of peripheral blood with in vivo infusions of TM-β1, we decided to examine the dynamics of peripheral blood cell profiles in detail primarily focusing on the two cell populations that are most sensitive to IL-15, namely CD8+T lymphocytes and NK cells, by flow cytrometry with continued TM-β1 administration. As shown in Fig. 3 quadrant percentages, there was considerable expansion of $CD8^+$ T as well as $CD8^+$ $NK1.1^+$ T cell subsets in $T3^b$-hIL-15 Tg mice (Fig 3., Panel A). It should be noted that the actual number of cells in each of these subsets including the NK cell subset, is even more dramatic when one takes into consideration that these mice have a 3-5 fold greater total number of white blood cells in their blood. More importantly, the blockade of IL-15 had an immediate and striking impact on the cells bearing the NK1.1 phenotypic marker resulting in the disappearance of these cells from the blood within the very first week after initiation of TM-β1 treatment. On the other hand, the impact on the massively expanded CD8+ T cells was more gradual though equally profound requiring a longer period of therapy for their elimination from the peripheral circulation. Intriguingly, even after 8 weeks of TM-β1 infusions, the $CD8^+$ T cell subset was reduced only to a level that was only slightly lower than those seen in the non-transgenic litter-mates (compare 9.17% versus 14%). This observation is consistent with previous studies, where administration of TM-β1 antibody while eliminated NK cells but had no meaningful impact on the CD8+ T lymphocytes in normal wild type mice (24, 25). This is also consistent with the observation in IL-15 knockout mice where there is only a modest reduction in the total CD8+ T cell population. In entertaining the possibility that within the CD8+ T cell population perhaps only a minor subset is exquisitely IL-15 dependent, we examined the modulation of CD44 high sub population of CD8+ T lymphocytes with TM-β1 treatment. As shown in Fig 3, Panel B, in $T3^b$-hIL-15 Tg mice, the expansion of peripheral blood lymphocytes was almost exclusively limited to the

CD8+CD44high subset and this was the population that was ablated by TM-β1 therapy. A parallel observation has been made in IL-15 knockout mice where $CD8^{+}CD44^{hi}$ cells were absent but $CD8^{+}CD44^{lo}$ populations were retained (26). Nonetheless, there appears to be a potential difference in naturally occurring $CD8+CD44^{hi}$ cells versus IL-15-induced $CD8+CD44^{hi}$ cells in response to TM-β1treatment since in treated animals, even after 8 weeks of antibody infusions, a treatment refractory population of $CD8+CD44^{hi}$ lymphocytes persisted. Although it remains unclear as to what accounts for these differences if any in IL-15 dependency in the two cell populations, it is important to note that the blockade of IL-15 signaling with TM-β1 eliminated only the fraction of CD8+ T cells that expanded under IL-15 influence and after treatment animals were still able to maintain normal numbers of CD8+ T lymphocytes. Of note, NK cells were also eliminated with IL-15 blockade. Therefore, a likely clinical implication of CD122 directed blockade of IL-15 is that only T lymphocytes that are vitally dependent on IL-15 are eliminated by this approach and the treatment is not likely to result in profound immunesuppression with total elimination of $CD8^{+}$ T lymphocytes.

Macroscopic and microscopic pathological changes in the intestines of $T3^{b}$-hIL-15 Tg mice are reversed by TM-β1 therapy: After 8 weeks of TM-β1 infusions, animals in all three groups were sacrificed for macroscopic and microscopic evaluation. At the time of necropsy, animals in all three groups were 8 months of age. As previously reported, in $T3^{b}$-hIL-15 Tg mice, the macroscopic evidence of intestinal inflammation usually become apparent when they were around 3 months of age. As shown in Fig. 4, Panel A, all $T3^{b}$-hIL-15 Tg mice that were in the untreated control group showed extensive macroscopic evidence of inflammation that was strikingly limited to the duodeno-jejunal region. There was extensive swelling and distention of the affected region with serosal hemorrhage and prominent distended blood vessels on the serosal surface. The serosal surface itself was dull and somewhat granular in appearance compared to the uniformly smooth and shiny serosal surface seen in the non-transgenic

litter-mates. However, no ulcerations or granulomatous lesions were noted in the intestines. In addition, as shown in Fig.4, Panel B, the mesenteric lymph nodes were massively enlarged along with the spleen of these $T3^b$-hIL-15 Tg mice. However, after 16 infusions of TM-β1 antibody over a period of 8 weeks all observed small intestinal macroscopic changes were reversed in all of the treated animals as can be seen in Fig.4, Panel A. In addition, TM-β1 treatment also was associated with the involution of massively enlarged spleen and mesenteric lymph nodes to their normal size in the treated animals (see Fig. 4, Panel B).

Having confirmed the reversal of gross pathologic changes of the intestines with TM-β1 treatment in $T3^b$-hIL-15 Tg mice, tissue sections were made from representative areas of the intestines for histologic evaluation as well. As previously reported, in $T3^b$-hIL-15 Tg mice, the microscopic abnormalities were strictly confined to the duodeno-jejunal area and included massive lymphocytic infiltration into the lamina propria even extending in some areas below the smooth muscle layer. Also there was significant intraepithelial lymphocytic infiltration as well, along with vacuolar degeneration of enterocytes especially at the tips of villi which were extensively blunted resulting in the markedly reduced ratio of villus to crypt height as shown in Fig. 5. However, in all $T3^b$-hIL-15 Tg mice that were treated with TM-β1 antibody there was a reversal of the entire spectrum of histologic changes including the re-establishment of normal villus heights that resembled those of non transgenic litter-mates as shown in Fig. 5.

TM-β1 antibody treatment re-establishes normal lymphocytic cell profiles in the small intestinal mucosa. It was indeed very remarkable to see that TM-β1 antibody reversed both gross pathological as well as histologic changes within a span of 8 weeks without leaving any of the florid persistent proximal small intestinal inflammation that was present in these $T3^b$-hIL-15 Tg mice. This remarkable resolution of the inflammation may likely have been facilitated at least in part by the high degree of tissue

remodeling and turn-over that is inherent to intestinal mucosa. More importantly, these observations also suggest that the local over-production of IL-15 by enterocytes *per se* is not injurious to the small intestinal mucosa since TM-β1 antibody has no impact on the synthesis of IL-15 and treated animals continued to locally express human IL-15 without any evidence of tissue injury as reflected by the unaltered serum human IL-15 in these animals during TM-β1 treatment (data not shown). Thus, it is the influx of lymphocytes in response to locally synthesized IL-15 that causes extensive tissue damage. Therefore, we decided to examine in more detail as to how TM-β1 treatment had impacted different subsets of T lymphocytes that accumulated in the proximal small intestines of $T3^b$-hIL-15 Tg mice by flow cytometry after collecting lymphocytes from the lamina proprial and the intraepithelial tissue fractions in euthanized animals after 8 weeks of TM-β1 antibody treatment. As previously reported (16), in $T3^b$-hIL-15 Tg mice, CD8+ T lymphocytes were increased in both the lamina proprial and intraepithelial compartments and a majority of these cells, particularly the lamina proprial CD8+ T cells were of memory phenotype with high expression levels of CD44 (see Fig. 6, Panel A). In addition, as seen in human celiac disease, there was a significant increase in $CD8^+$ T cells that co-expressed NK cell markers ($CD8^+NK1.1^+$), a subset of T cells that was virtually absent in the lamina propria of non-transgenic animals (fig.6, Panel B). In contrast, in non-transgenic animals, when T lymphocytes do express NK markers, usually they are of the $CD4^+$ type ($CD4^+NK1.1^+$) NK-T cells. However, in animals treated with TM-β1, these expanded $CD8^+CD44^{hi}$ as well as $CD8^+NK1.1^+$ cell populations were virtually eliminated from the lamina propria. Nonetheless, again as seen in peripheral blood, there appeared to be a small subpopulation of $CD8^+CD44^{hi}$ lymphocytes (~3%) in the lamina propria just as in non-transgenic animals that was refractory to TM-β1 treatment. However, the factors that account for their refractory nature to TM-β1 treatment remain to be fully defined. In previous studies (27) we noted that long term memory CD8+ T cells co-express IL-15Rα along with the IL-2/IL-15Rβ(CD122) and common γ

(CD132) subunits. Such cells that express the heterotrimeric receptors in *cis* are resistant to antibodies such as TM-β1 directed against β chain (CD122) in blocking IL-15 action. In the intraepithelial compartment of $T3^b$-hIL-15 Tg mice, the expanded cell population was primarily of TCR positive $CD8^+$ cell with α/α homodimers and these cells were markedly reduced by TM-β1 treatment as shown in Fig. 6, Panel C. The induction of killer cell receptor NKG2D in intestinal CD8+ T lymphocytes by locally synthesized IL-15 is pivotal in their tissue destructive activity in CD (5, 7, 8). As depicted earlier in Fig 1, Panel D, in $T3^b$-hIL-15 Tg mice, a greater proportion of LPL and IEL CD8+ T cells displayed NKG2D receptors on their cell surface. The expression of NKG2D and other NK cell-associated receptors on CD8+ T cells confers TCR-independent NK-like killing activity, cytokine secretion and proliferative activity in response to stress signals from epithelial enterocytes to such cells and these pathogenic T cells with NKG2D expression cause extensive tissue damage in a number of autoimmune diseases including rheumatoid arthritis, type 1 diabetes and CD (reviewed in ref 5). Importantly, with the TM-β1 treatment, these pathogenic CD8+ T cells in both intraepithelial compartment as well as lamina propial compartment were largely eliminated (compare Fig. 1, Panel D with Panel D of Fig. 6). Thus, from the phenotypic analyses of both peripheral blood as well as small intestinal mucosal lymphocytes the TM-β1 treatment resulted in the re-establishment of normal lymphocytic composition both in the intestinal mucosa as well as in the peripheral blood without causing any abnormal lymphocytopenia and attendant immunodeficiency.

It is clear from the data presented above that the TM-β1 antibody directed against the murine CD122 is very effective in reversing the progressive inflammatory changes in the proximal small intestines of $T3^b$-hIL-15 Tg mice while re-establishing normal lymphocyte profiles in the intestinal mucosa by eliminating the "pathogenic" CD8+ T lymphocytes that infiltrated the intestinal mucosa as a consequence of chronic persistent local over production of IL-15. A number of potential mechanisms

which are not necessarily mutually exclusive could be operational in preferentially eliminating these cells. One alternative is that the normal CD44 ^{hi} CD8+ cells might be long lived memory CD8+ T cells and might express all three chains of IL-15 receptor and may be resistant to the IL-15 blockade mediated by TM-β1, whereas cells dependent on high IL-15 concentrations might express IL-2/IL-15Rβ and γ_c but not IL-15Rα and these may be susceptible to IL-15 blockade. Another alternative is that the expanded CD8+ lymphocytes in T3^b-hIL-15 Tg mice could express greater density of surface CD122 than previously reported and hence likely to preferentially bind TM-β1 with greater affinity and avidity that can lead to their death either due to ADCC (antibody-dependant cellular cytotoxicity) or due to cytokine deprivation if these cells still require IL-15 for their survival and proliferation. However, if these CD8+ T cells no longer require IL-15 for their survival and proliferation, a possibility that is supported by the observations of Fehniger et al., (28) in their IL-15 transgenic animals that develop lymphocytic leukemia then ADCC might be the principal mechanism responsible for elimination of expanded CD8+T cells in TM-β1 treated animals. In examining this issue further, we assessed whether CD8+ T cells from our T3^b-hIL-15 Tg mice were capable of spontaneous proliferation *ex vivo* when cultured in medium without any added T cell growth factor cytokines. As can be seen in Fig. 7, Panel A, no meaningful proliferative differences were noted between CD8+ T lymphocytes from non transgenic litter-mates and CD8+T lymphocytes of T3^b-hIL-15 Tg mice. Furthermore when the culture medium was supplemented with IL-15, CD8+ lymphocytes from both groups displayed robust proliferation in response to IL-15 with a slightly higher level in T3^b-hIL-15 Tg mice that may likely result from having a higher surface density of CD122 on those cells (16). Having confirmed the dependence on IL-15 for the proliferation of CD8+ T cells from T3^b-hIL-15 Tg mice, we were interested in determining whether this expanded cell pool represented an aberrant clonal outgrowth of CD8+ lymphocytes or a global expansion of the natural CD8+ T cell repertoire of these animals. When we evaluated the TCR gene

rearrangement profiles of these cells by PCR amplification of the TCR Jβ2 region (28), the amplified fragment profile pattern of CD8+ lymphocytes from $T3^b$-hIL-15 Tg mice was similar to those of non transgenic litter mates as depicted in Panel B of Fig.7, thus revealing that the expansion of CD8+ T cells in $T3^b$-hIL-15 Tg mice, is in fact global and is not restricted to a particular aberrant clone.

In conclusion, here we present a proof-of-concept study to use IL-15 blockade as an effective treatment modality for the disordered IL-15/IL-15Rα expression that is associated with autoimmune intestinal damage in celiac disease. With the use of $T3^b$-hIL-15 Tg mice which mimic the autoimmune intestinal pathology orchestrated by locally synthesized IL-15 in celiac disease very closely, we have provided evidence that an antibody directed against the CD122 that blocks IL-15 signaling can effectively reverse the immunopathologic lesions in the proximal small intestines of these animals without causing any profound lymphocytopenia or immunodeficiency. This approach ablates the offending "pathogenic" CD8+ T lymphocytes at the apex of the pathological cascade rather than affecting downstream effector-mediators. A monoclonal antibody, MiK-(beta)1 that is directed against the human CD122 and blocks IL-15 activity is already in Phase I trials for evaluation in the treatment of T cell large granular lymphocyte leukemia (29) and the findings from the present study make a compelling rationale to explore whether this antibody MiK-(beta)1 or its humanized derivative Hu Mik-(beta)1 is of value in the treatment of celiac disease. Such a trial could be used to determine if disorders of the IL-15/IL-15 receptor system do indeed play a pivotal pathogenic role in CD and not merely correlate with the disease. This approach might be especially beneficial to patients with refractory celiac disease having a likely prognosis of developing life-threatening intestinal and extra-intestinal lymphomas for which no effective treatment exists at present.

Acknowledgments: This work was in part supported by the Intramural Research Program of the National Cancer Institute, Center for Cancer Research, NIH and Grants-in-Aid from the Ministry of Education, Science Culture and Sports, and a Grant-in-Aid for 2003 Multidisciplinary Research Project from MEXT in Japan. Seiji Yokoyama gratefully acknowledges support from the Japanese Foundation for AIDS Prevention, Tokyo, 101-0061, Japan. We also express our gratitude to Drs. James McKearney and Joe Harford at the Office of International Affairs, National Cancer Institute for their assistance and Celltech R&D Limited (now UCB Celltech), Slough, UK for their generous provision of TM-β1 antibody. We also thank Dr. Yutaka Tagaya for stimulating discussions.

Figure Legends:

Figure 1. Many pathognomonic features of human celiac disease are recapitulated in $T3^b$-hIL-15 Tg mice. (A) gross intestinal inflammation is confined to the proximal duodeno-jejunal region of the small intestine in $T3^b$-hIL-15 Tg mice. (B) H&E-stained section of small intestine of $T3^b$-hIL-15 Tg mice showing villous atrophy and massive intra-epthelial lymphocytic infiltration. Original magnification,×10. (C) Detection of Rae-1 expression in the small intestines of $T3^b$-hIL-15 Tg mouse by immunohistochemistry where Rae-1 expression is indicated by the presence of reddish brown precipitants. (D) Flow cytometry analysis of LPL and IEL isolated from the small intestine of $T3^b$-hIL-15 Tg or wild-trype mice reveals the presence of large numbers of pathogenic CD8+ T cells with NKG2D expression in $T3^b$-hIL-15 Tg mice.

Figure 2. Selective suppression of IL-15-induced proliferation of T lymphocytes by TM-β1 antibody in a dose-dependent manner. Mouse splenocytes ($1x10^5$ cells) were stimulated with 100ng/ml of human IL-15. Serial dilutions of TM-β1 antibody or an isotype control (rat IgG2b) were added. Cells were incubated for 72 hours and the proliferation of splenocytes was determined by a calorimetric assay.

Figure 3. TM-β1 antibody-mediated blockade of IL-15 activity reverses the abnormal peripheral blood lymphocytosis seen in $T3^b$-hIL-15 Tg mice in a dose and a time dependent manner. Peripheral blood mononuclear cells (PBMC) were isolated from WT, $T3^b$-hIL-15 Tg mice while undergoing antibody treatment longitudinally. The modulation

of CD8+ T cell subsets with NK and activation markers were assessed by flow cytometry. (A) CD8α and NK1.1 (B) CD8α and CD44 expression. Data shown are from one representative mouse from each group and the other mice displayed similar profiles.

Figure 4. TM-β1 antibody mediated blockade of IL-15 signaling completely reverses the macroscopic inflammatory pathologic lesions in $T3^b$-hIL-15 Tg mice. (A) small intestine (B) spleen and mesenteric lymph node. Data shown are from one representative mouse from each group and the other mice displayed similar profiles.

Figure 5. TM-β1 antibody mediated blockade of IL-15 signaling completely reverses the microscopic inflammatory pathologic lesions in $T3^b$-hIL-15 Tg mice. H&E stained sections of small intestine of WT, $T3^b$-hIL-15 Tg, and TM-β1 treated $T3^b$-hIL-15 Tg mice with original magnification at ×20. Data shown are from one representative mouse from each group and the other mice displayed similar profiles.

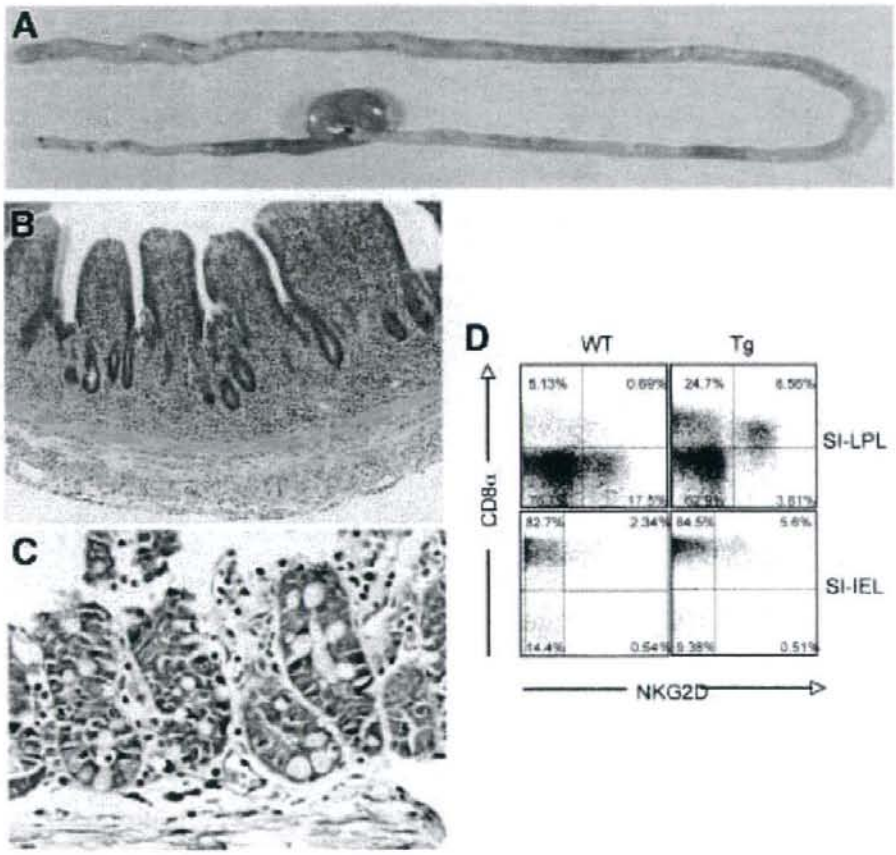
Figure 6. TM-β1 mediated blockade of IL-15 signaling virtually eliminated pathogenic and abnormal CD8+ T cell populations from small intestinal IEL and LPL of $T3^b$-hIL-15 Tg mice. LPL and IEL were isolated from the small intestines of WT, $T3^b$-hIL-15 Tg, and TM-β1 treated Tg mice, and subjected to surface phenotypic analysis by flow cytometry (A) Cell surface expression of CD44 and CD8α on LPL (B) Cell surface expression of CD8α and NK1.1 on LPL (C) Cell surface expression of CD3ε and CD8α on IEL were analyzed (left), $CD8\alpha^{high}$, $CD3\varepsilon^+$ cells were gated and analyzed for CD8β co-expression (right) (D) Cell surface expression of CD8α and NKG2D on LPL and IEL from small

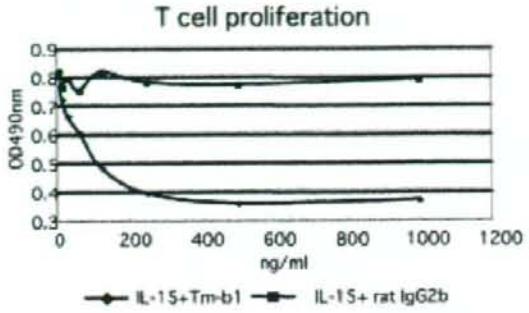
intestines of TM-β1 treated $T3^b$-hIL-15 Tg mice were analyzed by flow cytometry. Data shown are from one representative mouse from each group and the other mice displayed similar profiles.

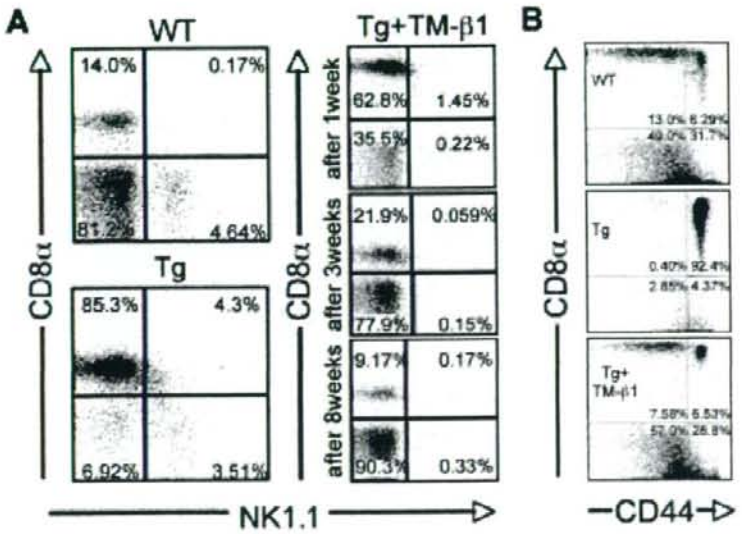
Figure 7. Proliferation of lymphocyte from $T3^b$-hIL-15 Tg mice is dependent on IL-15, and showed polyclonality. (A) Splenocytes were isolated from WT and $T3^b$-hIL-15 Tg mice, and these splenocytes were cultured in vitro with 50ng/ml of human IL-15 for 72 hours. Cell proliferation was analyzed by a colorimetric assay. (B) DNA PCR gel shows normal Jβ2 chain gene rearrangement on lymphocytes of $T3^b$-hIL-15 Tg mice. Lane 1:DNA marker, lane 2 through13 represent PBMC isolated from 12 different $T3^b$-hIL-15 Tg mice, lane 14: splenocytes from WT mouse, lane 15: splenocytes from $T3^b$-hIL-15 Tg mouse.

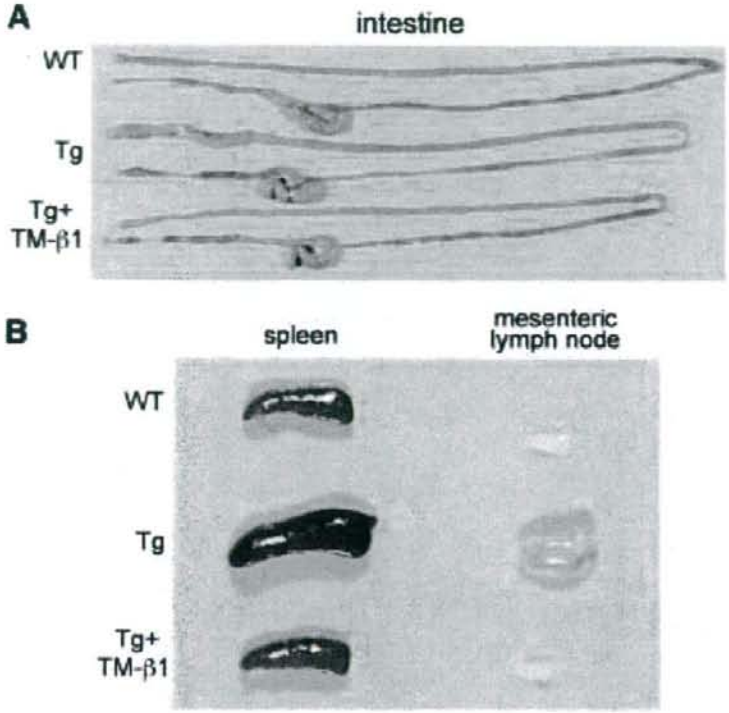
TABLE 1. Complete blood counts of peripheral blood collected longitudinally during TM-β1 antibody therapy.

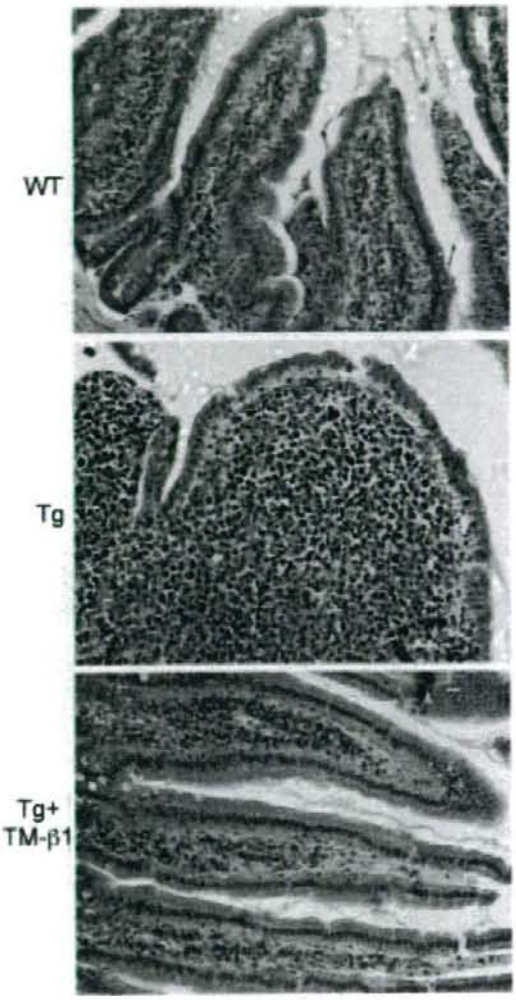
	WT	Transgenic	Transgenic treated with TM-β1 MAb	
			Rx for 3 wks	Rx for 8 wks
WBC	$8.1x10^3/\mu L$	$4.9x10^4/\mu L$	$9.7x10^3/\mu L$	$1.2x10^4/\mu L$
RBC	$1.1x10^7/\mu L$	$9.92x10^6/\mu L$	$9.80x10^6/\mu L$	$1.0x10^7/\mu L$
HGB	15.4 g/dL	14.6x g/dL	14.0 g/dL	14.3 g/dL
HCT	53.6%	50.8%	50.5%	51.8%
MCV	51.2 fL	51.2 fL	51.5 fL	51 fL
MCH	14.7 pg	14.7 pg	14.3 pg	14.1 pg
MCHC	28.7 g/dL	28.7 g/dL	27.7 g/dL	27.7 g/dL
PLT	$1.0x10^6/\mu L$	$8.8x10^5/\mu L$	$8.0x10^5/\mu L$	$1.5x10^6/\mu L$

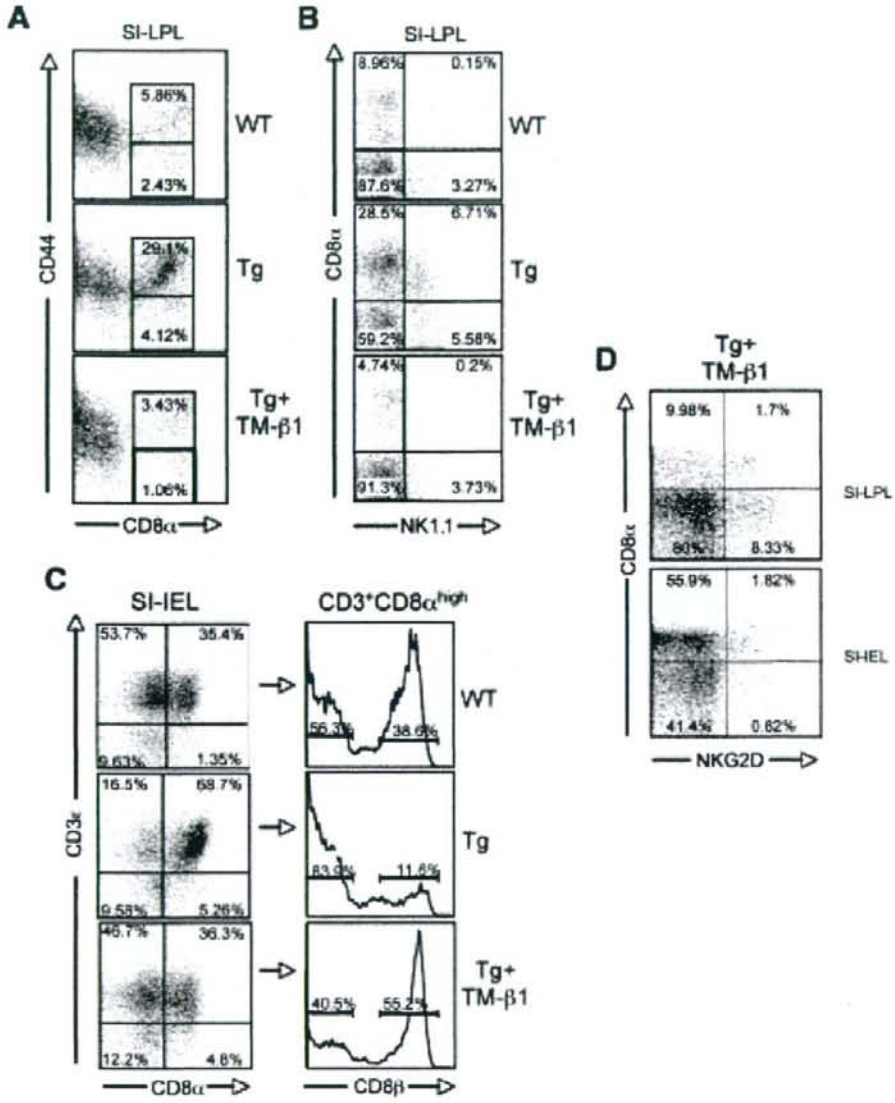

A
B
C
D
WT
Tg
5.13%
0.69%
24.7%
6.50%
SI-LPL
82.7%
2.34%
84.5%
5.6%
SI-IEL
14.4%
0.54%
9.38%
0.51%
CD8α
NKG2D

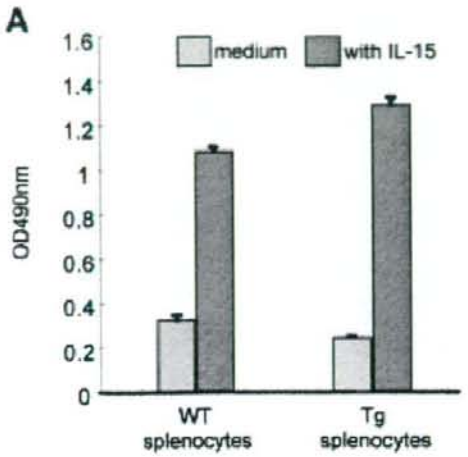

T cell proliferation
OD490nm
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
200
400
600
800
1000
1200
ng/ml
IL-15+Tm-b1
IL-15+ rat IgG2b

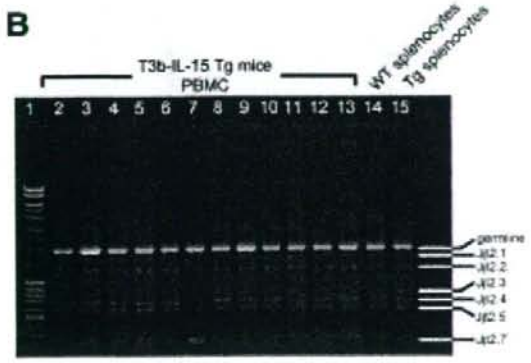

A
WT
Tg+TM-β1
14.0%
0.17%
81.2%
4.64%
Tg
85.3%
4.3%
6.92%
3.51%
after 1week
62.8%
1.45%
35.5%
0.22%
after 3weeks
21.9%
0.059%
77.9%
0.15%
after 8weeks
9.17%
0.17%
90.3%
0.33%
CD8α
NK1.1
B
WT
Tg
Tg+
TM-β1
CD8α
CD44


A
intestine
WT
Tg
Tg+
TM-β1
B
spleen
mesenteric
lymph node
WT
Tg
Tg+
TM-β1


WT
Tg
Tg+
TM-β1


A
SI-LPL
5.86%
2.43%
WT
29.1%
4.12%
Tg
3.43%
1.06%
Tg+
TM-β1
CD44
CD8α
B
SI-LPL
8.96%
0.15%
87.6%
3.27%
WT
28.5%
6.71%
59.2%
5.58%
Tg
4.74%
0.2%
91.3%
3.73%
Tg+
TM-β1
CD8α
NK1.1
C
SI-IEL
CD3+CD8αhigh
53.7%
35.4%
9.63%
1.35%
WT
16.5%
68.7%
9.58%
5.26%
Tg
46.7%
36.3%
12.2%
4.8%
Tg+
TM-β1
CD3ε
CD8α
CD8β
D
Tg+
TM-β1
9.98%
1.7%
80%
8.33%
SI-LPL
55.9%
1.82%
41.4%
0.82%
SI-IEL
CD8α
NKG2D


A
medium
with IL-15
OD490nm
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
WT splenocytes
Tg splenocytes


B
T3b-IL-15 Tg mice PBMC
WT splenocytes
Tg splenocytes
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
germline
Jt2.1
Jt2.2
Jt2.3
Jt2.4
Jt2.5
Jt2.7

References

1. Kagnoff M. F. Celiac Disease:pathogenesis of a model immunogenetic disease. 2007. J. Clin. Invest. 117:41-49.

2. Sollid LM, Jabri B.2005. Is celiac disease an autoimmune disorder? Curr Opin Immunol. 17:595-600.

3. Catassi C, et al., 2007. Detection of Celiac disease in primary care: a multicenter case-finding study in North America. Am J Gastroenterol. 102:1454-60.

4. Dewar DH, Ciclitira PJ. 2005. Clinical features and diagnosis of celiac disease. Gastroenterology. 128(4 Suppl 1):S19-24.

5. Jabri B, Sollid LM. 2006. Mechanisms of disease: immunopathogenesis of celiac disease. Nat Clin Pract Gastroenterol Hepatol. 3:516-25.

6. Marsh MN. 1992. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology. 102:330-54.

7. Hüe S, et al., 2004. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. Immunity.21:367-77.

8. Meresse B, et al., 2004. Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease. Immunity. 21:357-66.

9. Maiuri L, Ciacci C, Auricchio S, Brown V, Quaratino S, Londei M. 2000. Interleukin 15 mediates epithelial changes in celiac disease. Gastroenterology.119:996-1006.

10. Mention JJ et al., 2003. Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. Gastroenterology. 125:730-45.