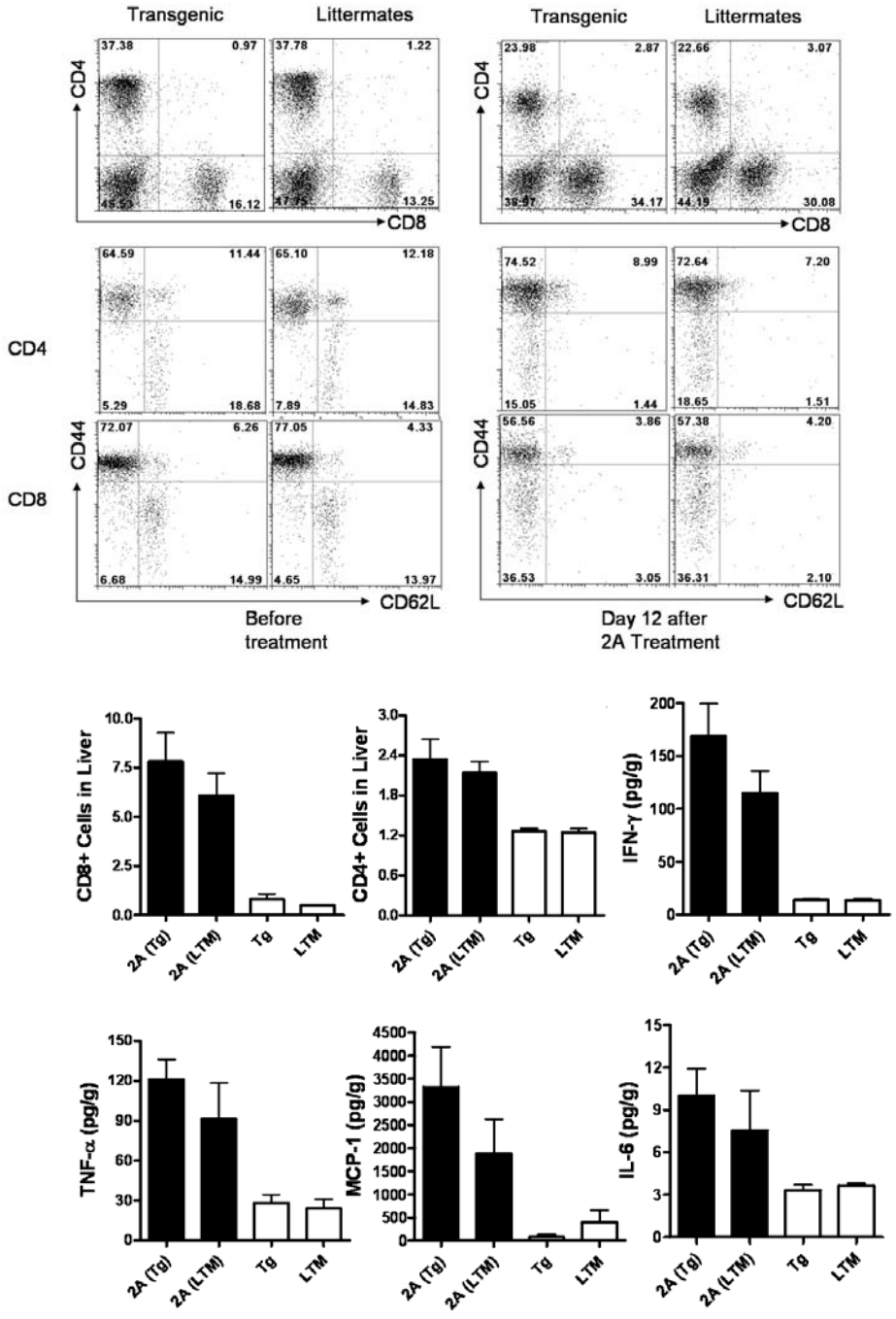
Supplemental Materials

Table 1. ***Characteristics of the populations enrolled in the study***

	Patients		
	HC	CHB/ Non-LC	CHB/ LC
Cases	31	21	40
Age (years)	30(21-55)	31(19-53)	48 (16-68)
Gender (male/female)	16/15	10/11	23/17
Plasma HBV DNA (Copies/ml)	U.D.	$2.8x10^7$	$5.4x10^3$
Plasma ALT (U/L)	11 (2-25)	28 (3-62)*	23 (3-164)*
Plasma T.Bili (μmol/L)	23 (16-30)	19 (14-37)	42 (8-328)
Plasma IL-8 (pg/ml)	13 (5-41)	13 (6-23)	44 (6-183)*
Plasma IL-6 (pg/ml)	5(3-10)	6(3-8)	10(4-33)*
Plasma TNF-α (pg/ml)	5(0-13)	6(3-10)	6(0-15)
Plasma IFN-γ(pg/ml)	1.1(0-3)	1.6(0-4)	3.2 (0-18)*
Plasma PIIINP (μg/ml)	35(16-85)	88 (0-180)*	165 (22-1341)*
Plasma HA (ng/ml)	33 (0-78)	44 (12-110)	745 (22-5332)*
Plasma CIV (ng/ml)	12 (0-47)	4 (0-23)	23 (6-87)*

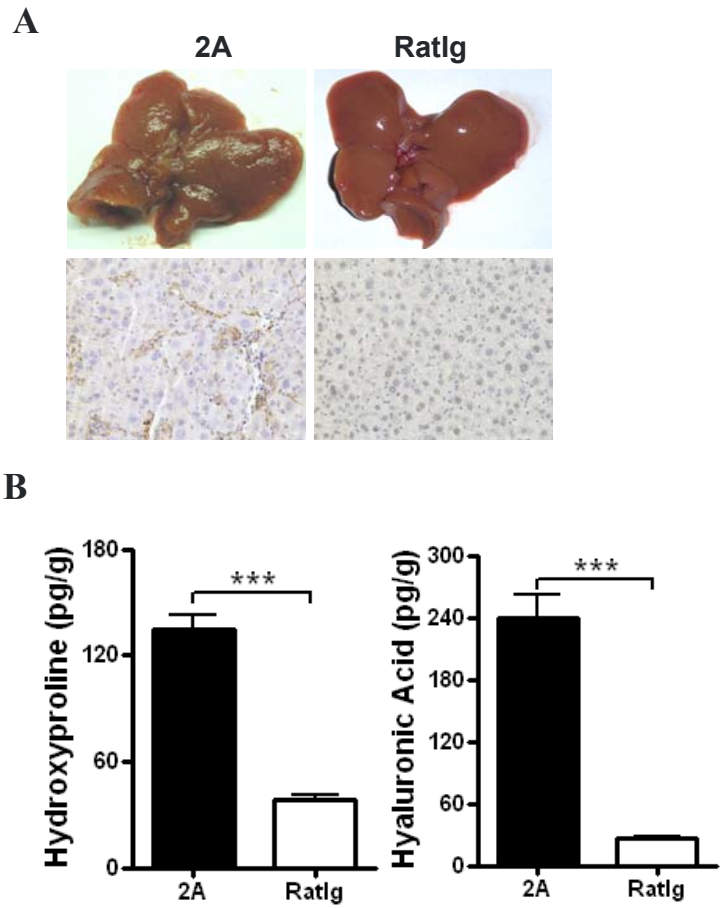
Data are shown as median and range.*, $P<0.05$, compared with HC group.
U.D. Undetected.

Supplemental Figures

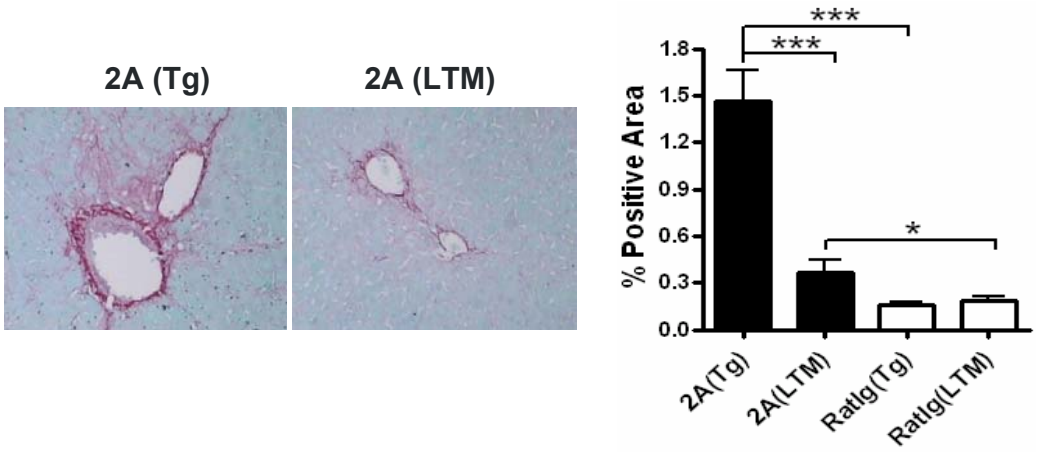


Supplemental Figure 1. Marginal difference in the percentage and total number of the CD4 and CD8 positive cells in the IHLs. HBV transgenic mice (Tg) or wild type littermates (LTM) were injected i.p. weekly with 100μg agonist CD137 mAb or control RatIg since day 0. The intrahepatic lymphocytes (IHLs) were isolated for FACS staining and the hepatic cytokines were

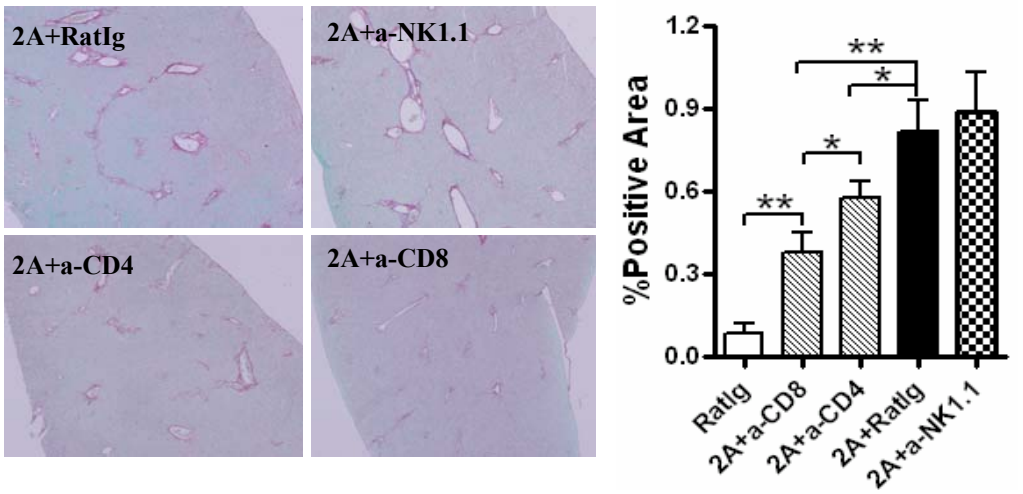
determined by ELISA before and day 12 after anti-CD137 mAb treatment. The CD44+ CD62L- cells gated in the CD4+ or CD8+ cells.



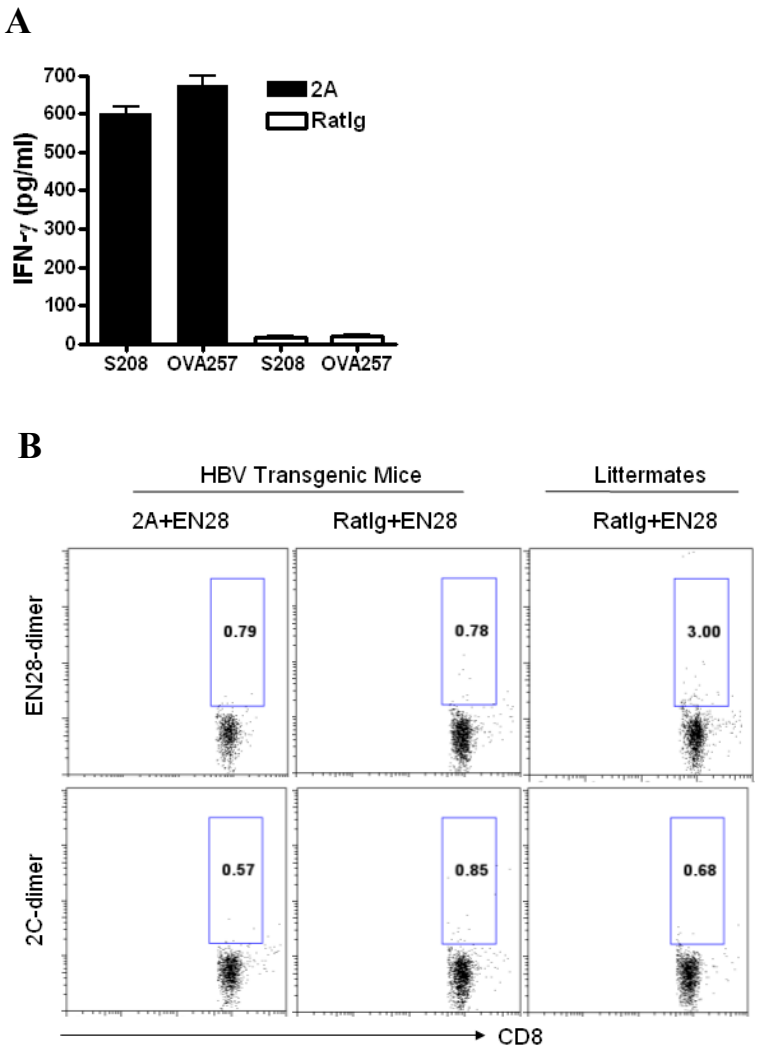
Supplemental Figure 2. Characterization of liver fibrosis after anti-CD137 injections. HBV transgenic mice (Tg) were injected i.p. weekly with 100ug agonist CD137 mAb (Clone 2A) or control RatIg since day 0. One week after the fifth injections, the mice were sacrificed. **(A)** The representative liver figures (up) and liver sections with anti-SMA staining (down) were shown; **(B)** The hydroxyproline or hyaluronic acid was detected in liver homogenates.



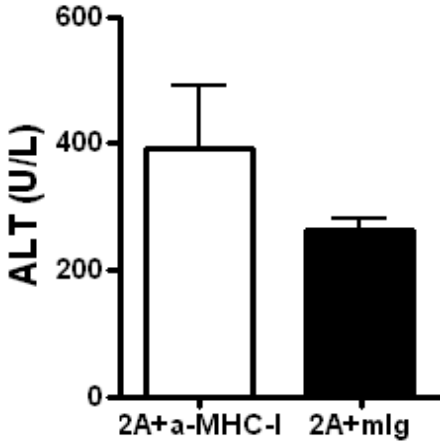
Supplemental Figure 3. Severe fibrosis induction in HBV transgenic mice compared with wild type littlermates. Liver sections (left) from transgenic mice and wild type littermates 1 week following the fifth weekly anti-CD137 mAb or RatIg injections were performed with Sirius Red staining and then further quantified (right) by image systems.



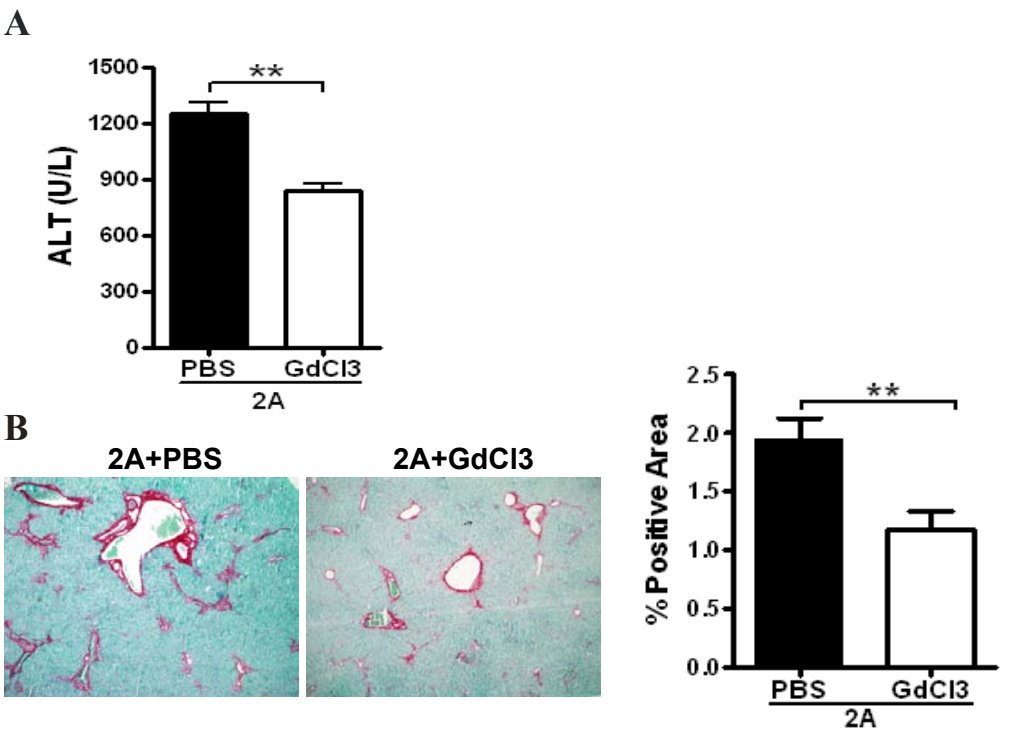
Supplemental Figure 4. Attenuated liver fibrosis by CD8 depletion. HBV transgenic mice were treated i.p. with 100ug depletion antibodies for CD8, CD4 or NK1.1 or control antibody at day -1, and followed by twice a week to maintain the effect of cell depletion. Anti-CD137 mAb was injected i.p. weekly at day 0. Sirius Red staining was performed on the liver sections from the recipient mice 1 week after the fifth anti-CD137 mAb injection (left) and the positive areas was quantified by image systems (right)**.** One representative result from at least 2 independent experiments is shown. *, $P<0.05$, **, $P<0.01$.



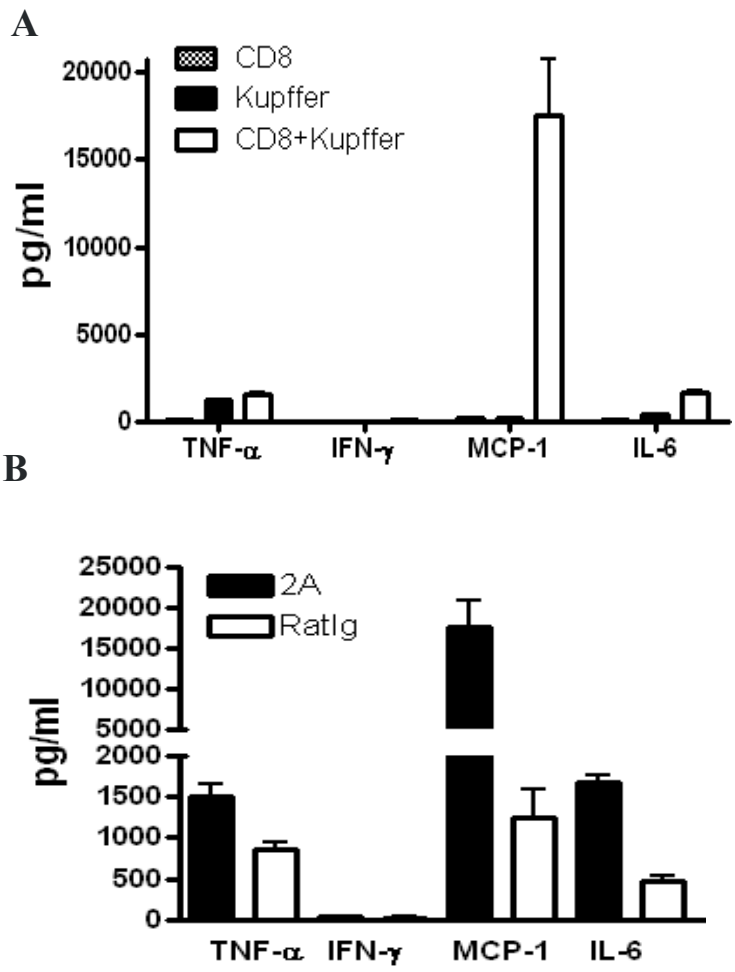
Supplemental Figure 5. Detection of HBsAg specific T cell responses in HBV transgenic mice treated with anti-CD137. (**A**) HBV transgenic mice were treated with anti-CD137 mAb (2A) or RatIg at day 0 and day 7. At day 12, splenocytes and IHLs were co-cultured in 24-well plates with HBsAg peptide s208 (OVA257 peptide served as negative control) in the presence of IL-2 (30U/ml, ebioscience) for 5 days. IFN-γ in the culture media was detected by ELISA. **(B)** Both HBV transgenic F1 (H-2^{bxd}) mice and wild type littermates were immunized with EN28 peptide and polyI:C at day -5 and day 9 and further treated with anti-CD137 or RatIg at day 0 and day 7. At day 12, splenocytes and IHLs were co-cultured in 24-well plates with EN28 or control 2C peptide in vitro for 48 hours, and then stained with EN28-dimer and 2C-dimer.



Supplemental Figure 6. The effect of MHC class I blockade in anti-CD137 mAb-induced liver injury. HBV transgenic mice were given anti-MHC-I blocking antibody (300ug per mice) twice a week from day -1, and followed by weekly 2A injections from day 0. Shown are the serum ALT levels at day 12.



Supplemental Figure 7. The role of liver Macrophage in hepatic fibrosis. HBV transgenic mice were treated weekly with anti-CD137 mAb at day 0 and followed by injections of 200ul (1mg/ml) GdCl3 or PBS twice a week since day 4. **(A)** At day 12, serum ALT activities were examined. **(B)** The mice were sacrificed 1 week after fifth mAb injections and the liver sections were performed with Sirius red staining (Left) and then further quantified by image systems (Right). One representative result from at least 2 independent experiments is shown. *, $P<0.05$, **, $P<0.01$.



Supplemental Figure 8. Co-culture of CD8 and macrophage promotes MCP-1 production. HBV transgenic mice were treated with anti-CD137 or RatIg weekly and sacrificed at day 12. Intrahepatic CD8+ and CD11b+ cells were purified by MACS. $2x10^5$ CD8+ cells were stimulated with 0.3ug/ml immobilized anti-CD3 and 1x10e5 CD11b+ macrophage were cultured alone or both were co-cultured in 96-well plates in triplicate for 48hrs. Cytokine levels in the culture media was determined by CBA. (A) Cytokines produced by the purified cells from anti-CD137-treated transgenic mice were shown; (B) Comparison of cytokine levels in the co-culture of CD8+ and CD1b+ cells between anti-CD137 and control Ig treated mice.