

## Supplemental Table1: Murine HLH Disease Severity Scoring System

In order to more accurately measure disease severity in LCMV-infected mice, we have developed a clinical scoring system ranging from 0 (asymptomatic) to 15 based on weight loss (0-3), stance (0-3), coordination (0-3), skin tenting (0-2), conjunctivitis (0-2), ascites (0-2), and mortality (cumulative score 12). LCMV-infected prf-/- mice experience exaggerated symptomatology over time yielding high clinical scores before becoming moribund, defined as a clinical score 11 or greater. In contrast, LCMV-infected wild-type C57BL/6 mice (WT) experience mild weight loss and clinical symptoms, generally recovering by day 15 of illness.

	SCORE	Consistent Findings
<b>Weight loss (0-3)</b>	0	< 5% weight loss
	1	5% - 10% weight loss
	2	10% - 15% weight loss
	3	>15% weight loss

<b>Stance (0-3)</b>	0	Smooth, well groomed fur
	1	Ruffled, unkempt fur
	2	Hunched back, unable to straighten out
	3	Huddled and shaking; minimal activity

**Coordination (0-3)** Assessed by twirl test (twirl mouse 3X over cage and gently drop mouse in center of cage). Sometimes it is necessary to repeat or make sure there is at least 1 companion mouse in the “drop in” cage to provide a visual cue. Should not allow more than 2 companion mice in “drop in” cage to minimize crowding effect.

0	Moves quickly to corner without direction change
1	Hesitation, but goes to corner without direction change
2	May hesitate; Goes to a corner within 5 seconds, but changes direction on the way
3	Does not make it to a corner within 5 seconds; usually huddled, shaking or walking in circles

<b>Skin tenting (0-2)</b>	Assessed by pinch test (pinch mouse skin on chest and observe skin tenting)	
	0	None; skin snaps back into place
	1	Skin initially tents, but returns to normal by 3 seconds
	2	Skin remains tented after 3 seconds

<b>Conjunctivitis (0-2)</b>	0	None
	1	Crusting of 1 eye
	2	Crusting of 2 eyes <b>(Sacrifice mouse)</b>

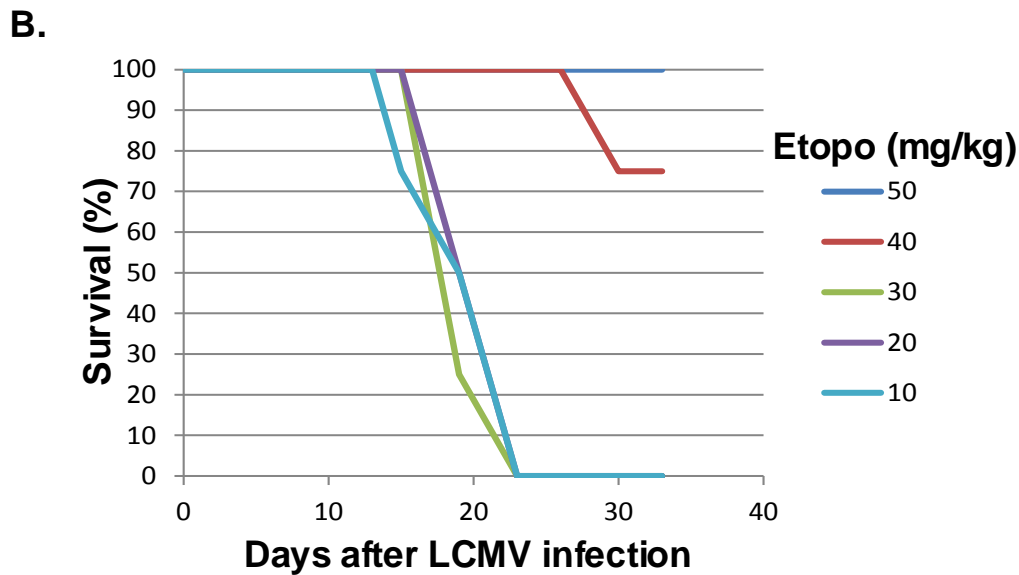
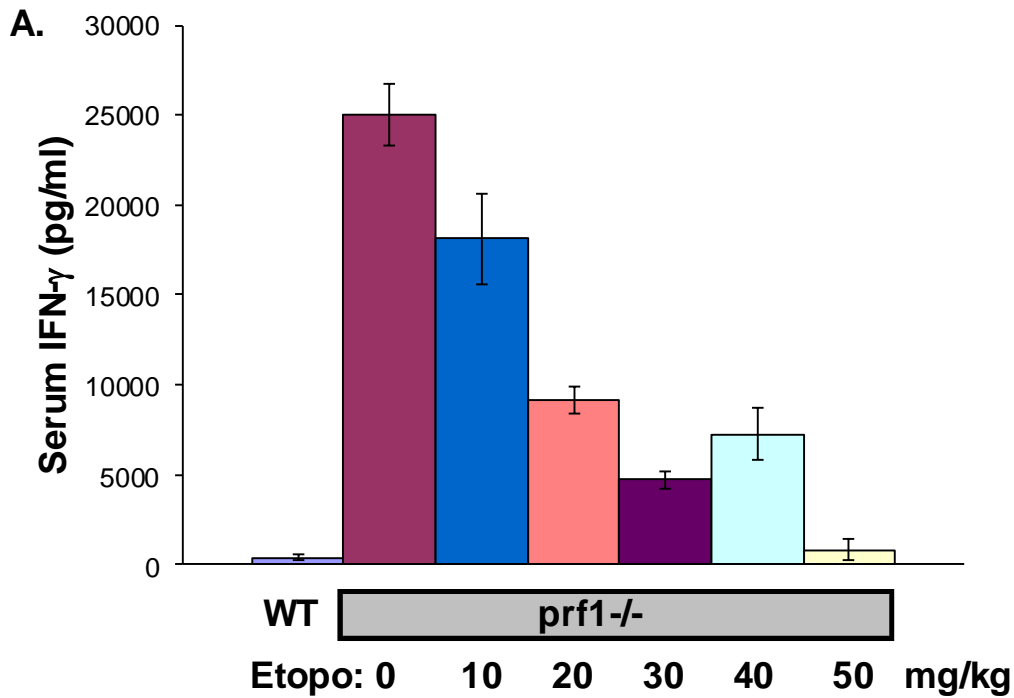
<b>Ascites (0-2)</b>	0	None; abdomen remains depressed after palpation
	1	Full abdomen that <u>may</u> represent ascites
	2	Definitive and/or massive ascites

### Moribund (cumulative score 11)

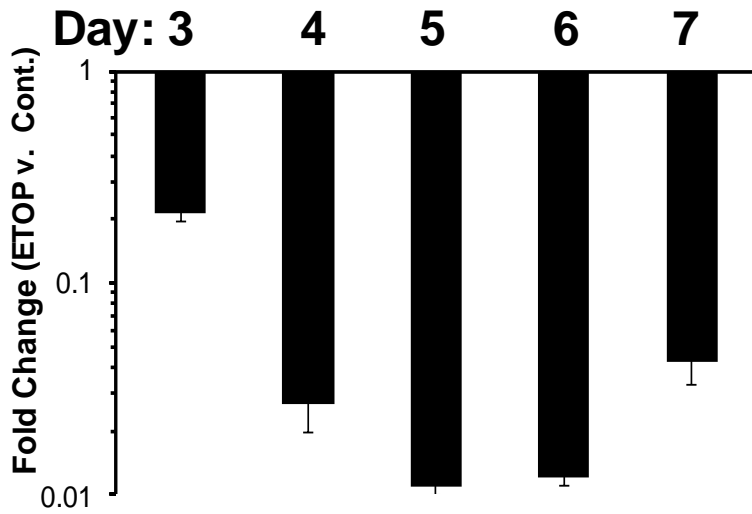
Mice achieving a cumulative score of 11 on 2 sequential daily assessments are considered moribund and **sacrificed**. Any mouse unable to move adequately so that it cannot eat or drink, or with weight loss >20% is considered moribund and is sacrificed without a second assessment.

### Mortality (cumulative score 12)

Dead mice are assigned a cumulative score of 12 for analysis purposes.



**Supplemental Figure 1. Dose:response relationship for etoposide as a therapeutic agent in murine HLH. A.** *Prf*<sup>-/-</sup> mice were treated on day 5 of LCMV infection with etoposide at the indicated doses. Day 8 serum IFN- $\gamma$  levels were determined by ELISA. WT mice are shown for comparison. **B.** Survival in this cohort was determined.



**Supplemental Figure 2. Timing and efficacy of etoposide for ablation of activated T cells.** LCMV-infected *prf*<sup>-/-</sup> mice were treated with etoposide (50mg/kg ip) at the indicated day post infection. LCMV-specific CD8<sup>+</sup> T cells (D<sup>b</sup>-GP33 tetramer<sup>+</sup>) were enumerated in the spleen on day 8 after infection. The fold change compared to carrier treated controls is plotted.