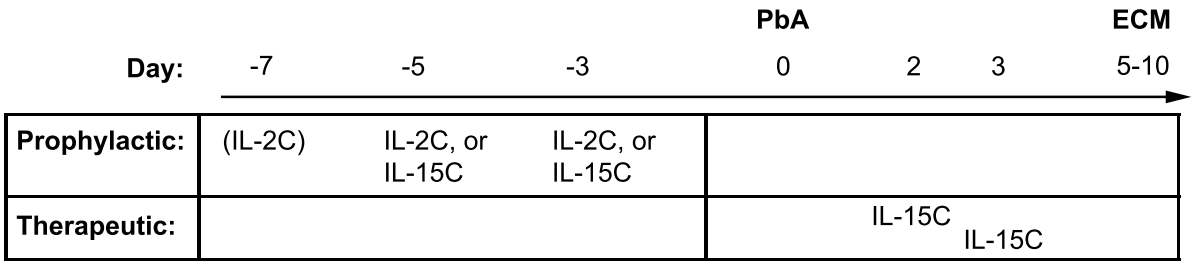

Figure S1. Schematic of the timing of therapeutic versus prophylactic treatment, PbA infection, and development of ECM. For prophylactic treatments, mice were given three injections of IL-2C i.v. on days -7, -5, and -3 in some experiments or two injections on days -5 and -3 relative to PbA infection; other mice were given two injections of IL-15C on days -5 and -3 relative to PbA infection. For therapeutic treatments, mice were given two injections of IL-15C i.v. on days 2 and 3 post-PbA infection. Related to Figure 1.

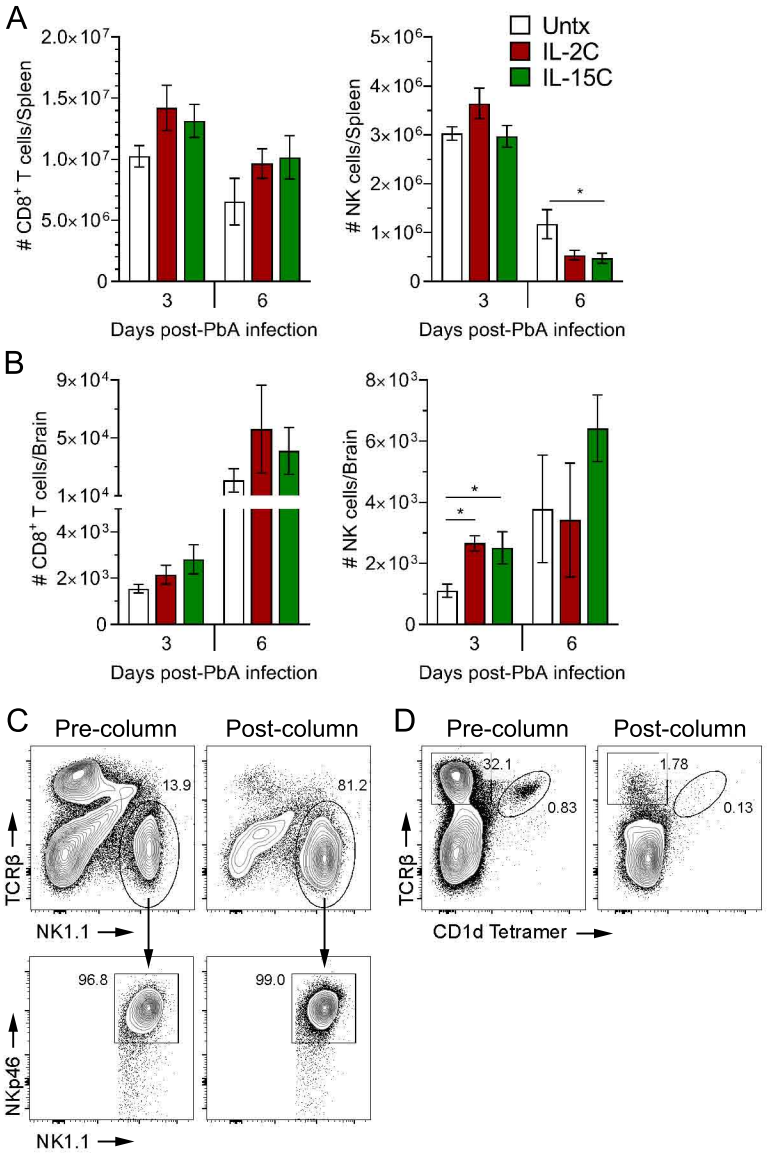

Figure S2. CD8+ T cell and NK cell numbers post-PbA infection, and purity of cytokine complex-treated NK cells. (A-B) Mice were left untreated or treated with IL-2C or IL-15C on days -5 and -3 relative to PbA infection. Number of CD8+ T cells and NK cells in the spleen (A) and brain (B) on days 3 or 6 pi. Data are combined from two independent experiments and presented as mean ± SEM. * $P < 0.05$ as determined by one-way ANOVA followed by Tukey's multiple comparison test. (C-D) Gating strategy for identifying NK cells (C) or T and NKT cells (D) from splenocytes from IL-15C-treated mice before and after NK cell enrichment. Related to Figure 2.

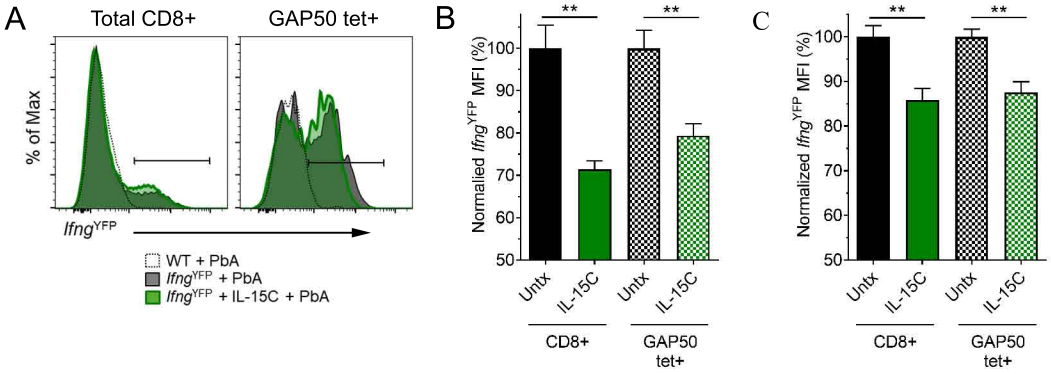

Figure S3. IL-15C treatment results in reduced IFN-γ production by CD8+ T cells in the spleen and blood on day 6 pi. Blood and brains of PbA-infected *Ifng*^{YFP} mice that were left untreated (n=6) or treated with IL-15C (n=7) were harvested on day 6 pi. Infiltrating leukocytes were analyzed by flow cytometry to assess *Ifng*^{YFP} MFI expression. (A) Representative histograms of *Ifng*^{YFP} expression in splenic CD8 T cells or GAP50-specific CD8+ T cells. Quantification of the normalized *Ifng*^{YFP} MFI expression in CD8+ T cells from the spleen (B) or blood (C). Data are combined from two independent experiments and presented as the mean ± SEM. ** $P < 0.01$ as determined by two-way student's *t* test. Related to Figure 4.

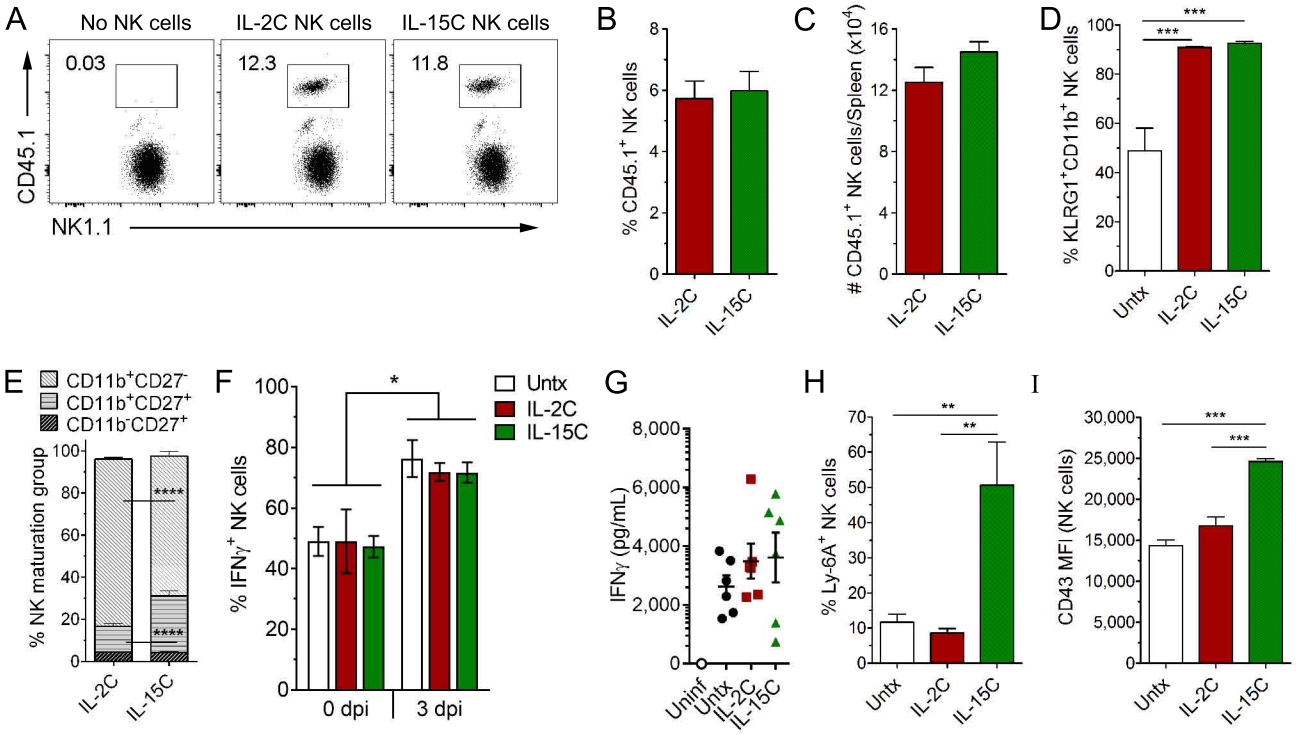

Figure S4. Comparison of IL-15C- and IL-2C-treated NK cells. NK cells were enriched from the spleens of mice treated with three times with IL-2C or twice with IL-15C and transferred into congenically mis-matched recipients (n=5 recipients/group). The next day, spleens were harvested for analysis of the presence of transferred NK cells. (A) Representative dot plots demonstrating the gating strategy to identify transferred CD45.1+ NK cells. The frequency (B) and total number (C) of transferred NK cells in the spleen. Data are combined from two independent experiments and presented as the mean ± SEM. (D,E,H,I) Mice were left untreated or treated twice with IL-2C or IL-15C (n=5-7/group), and the activation phenotype of splenic NK cells were analyzed three days after the second treatment by flow cytometry. Data are combined from two independent experiments and presented as the mean ± SEM. (D) The frequency of KLRG1+CD11b+ NK cells was quantified. (E) Chiossone and colleagues (2009) identified a four-stage maturation program for NK cells using CD27 and CD11b to distinguish immature and mature NK cells: CD27-CD11b- NK cells are immature, and they mature progressively to become (1) CD27+CD11b-, (2) CD27+CD11b+, (3) CD27-CD11b+. CD27+CD11b+ and CD27-CD11b+ NK cells were most strongly associated with effector functions (Chiossone et al., 2009). The frequency of each NK cell maturation stage was quantified. *** $P < 0.001$ as determined by two-way ANOVA followed by Bonferroni post-test. (F) Mice were left untreated or treated twice with IL-2C or IL-15C (n=3/group). On days 0 or 3 post-PbA infection, splenocytes were stimulated ex vivo with IL-12 and IL-18, and the frequency of IFNγ-producing NK cells was quantified. Data are representative of two independent experiments. * $P < 0.05$ as determined by two-way ANOVA followed by Bonferroni post-test. (G) Serum levels of IFN-γ on day 5 post-PbA infection were measured from mice left untreated or treated prophylactically with IL-2C or IL-15C. An uninfected mouse served as a control. Each dot represents an individual mouse. Data are combined from two independent experiments. (H-I) Following IL-2C or IL-15C treatment, the phenotype of splenic NK cells was analyzed: the frequency of Ly-6A+ NK cells was quantified (H), and the MFI of CD43 was quantified (I). (D,H,I) ** $P < 0.01$, *** $P < 0.001$ as determined by one-way ANOVA followed by Tukey's multiple comparison test. Related to Figure 5.

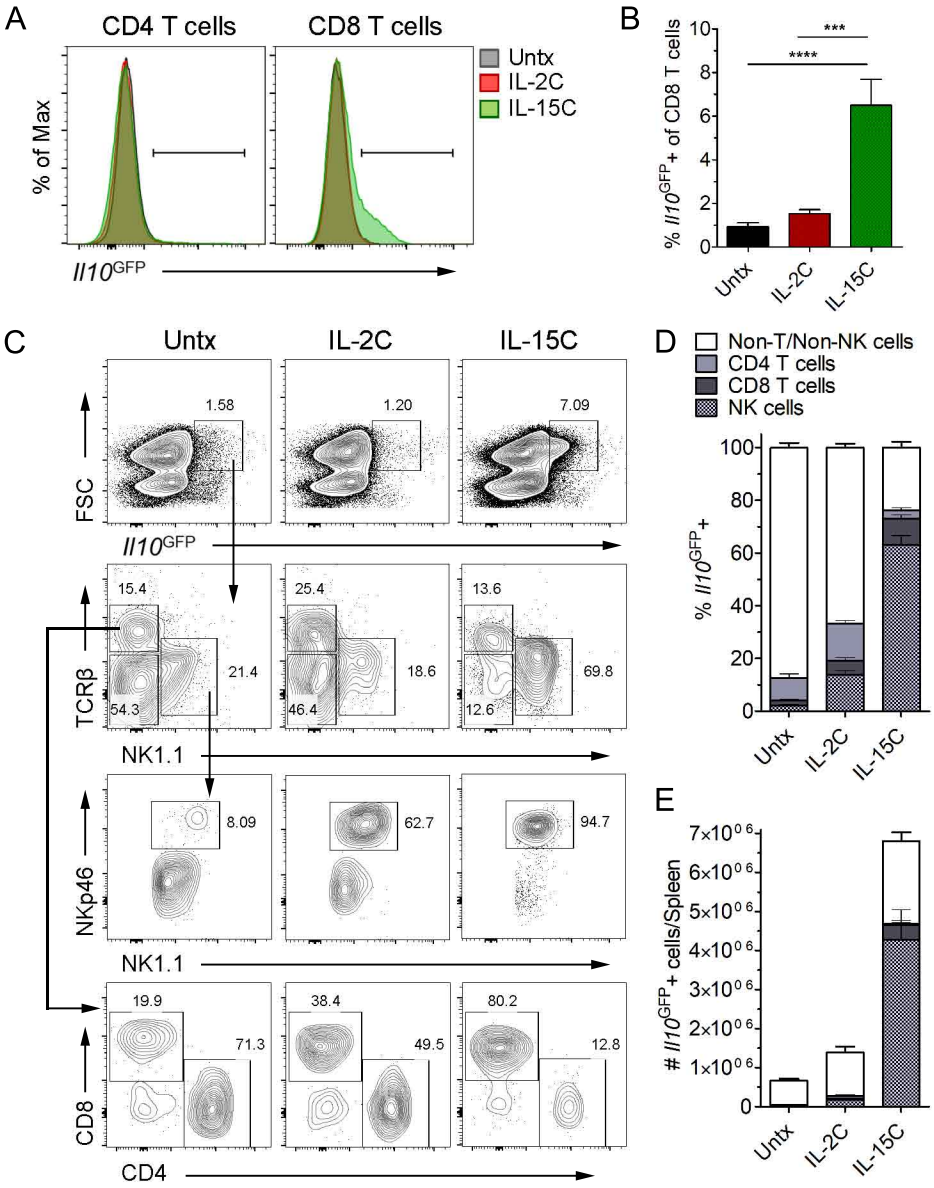

Figure S5. NK cells are the major IL-10+ cell type following IL-15C treatment. *Il10*^{GFP} mice were left untreated (n=11) or treated twice with IL-2C (n=8) or IL-15C (n=11); three days after the second treatment, cells in the spleen were analyzed by flow cytometry. (A) Representative histograms of *Il10*^{GFP} expression in TCRβ+CD4+ or TCRβ+ CD8+ cells, which is quantified in (B). *** $P < 0.001$, **** $P < 0.0001$ as determined by one-way ANOVA followed by Tukey's multiple comparison test. (C) Gating strategy for identifying *Il10*^{GFP}+ NK cells, CD8 T cells, CD4 T cells, and non-T/non-NK cells. The frequency (D) and total number (E) of *Il10*^{GFP}+ NK cells, CD8 T cells, CD4 T cells, and non-T/non-NK cells were quantified. Data are combined from four independent experiments and presented as the mean ± SEM (B, D, E). Related to Figure 5.

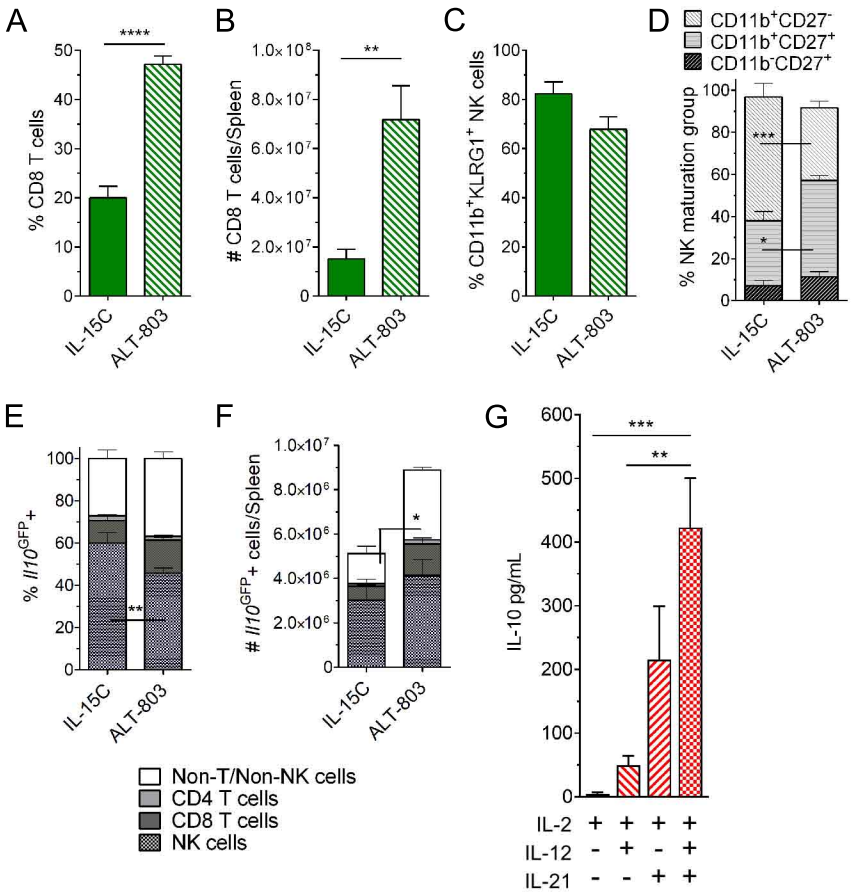

Figure S6. Human IL-15C treatment results in similar NK cell activation as mouse IL-15C treatment. *Il10*^{GFP} mice were treated twice with IL-15C (n=4) or ALT-803 (n=5); three days after the second treatment, cells in the spleen were analyzed by flow cytometry. The frequency (A) and number (B) of CD8+ T cells were quantified. After gating on NK1.1+NKp46+TCRβ- NK cells, the frequency of KLRG1+CD11b+ cells (C) and maturation state (D) were quantified. Based on the gating strategy shown in Figure S5, the frequency (E) and total number (F) of *Il10*^{GFP}+ NK cells, CD8+ T cells, CD4+ T cells, and non-T/non-NK cells were quantified. Data are combined from two independent experiments and presented as the mean ± SEM. (A-B) ** $P < 0.01$, **** $P < 0.0001$ as determined by two-way student's *t* test. (D-F) ** $P < 0.01$, **** $P < 0.0001$ as determined by two-way ANOVA followed by Bonferroni post-test. (G) Primary human NK cells (n = 10 donors) were cultured for 6 days in the presence IL-2 with or without IL-21 and with or without addition of IL-12 24 h prior to harvest. IL-10 in the supernatant was quantified. Data are combined from three independent experiments and represented as the mean ± SEM. ** $P < 0.01$, *** $P < 0.001$ as determined by one-way ANOVA followed by Tukey's multiple comparison test. Related to Figure 6.

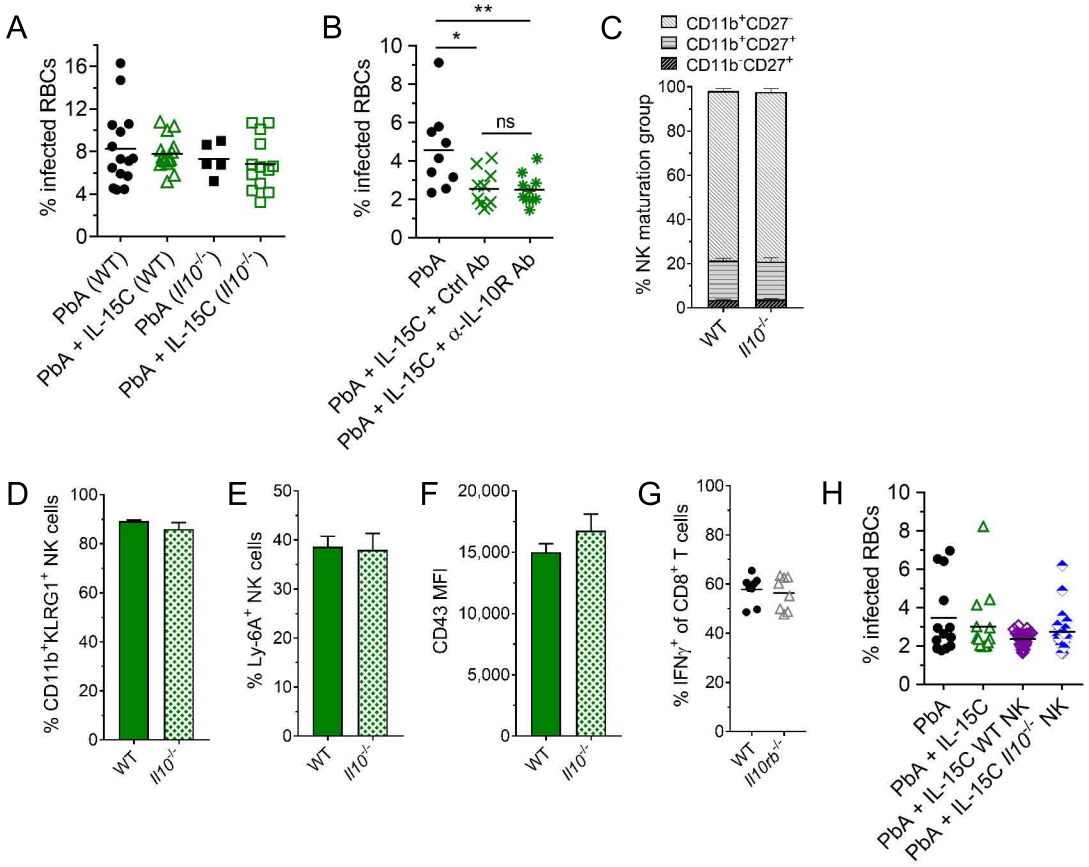

Figure S7. Parasitemia levels do not correlate with survival from ECM. (A) Parasitemia analysis on day 6 pi from mice in Figure 6A. (B) Parasitemia analysis on day 6 pi from mice in Figure 6B. (C-F) WT and *Il10*$^{-/-}$ mice were treated twice with IL-15C; three days after the second treatment, cells in the spleen were analyzed by flow cytometry for NK cell maturation markers (C) and surface expression of CD11b and KLRG1 (D), Ly-6A (E), and CD43 (F). (G) WT and *Il10rb*$^{-/-}$ CD8+ T cells were transferred into congenically disparate WT mice on day -6, treated with IL-15C on days -5 and -3, and infected with PbA on day 0. Frequency of IFN-γ+ WT or *Il10rb*$^{-/-}$ CD8+ T cells in the brain on day 6 pi. (H) Parasitemia analysis on day 6 pi from mice in Figure 6C. Horizontal bar indicates the mean. * $P < 0.05$, ** $P < 0.01$ as determined by one-way ANOVA followed by Tukey's multiple comparison test. Related to Figure 7.