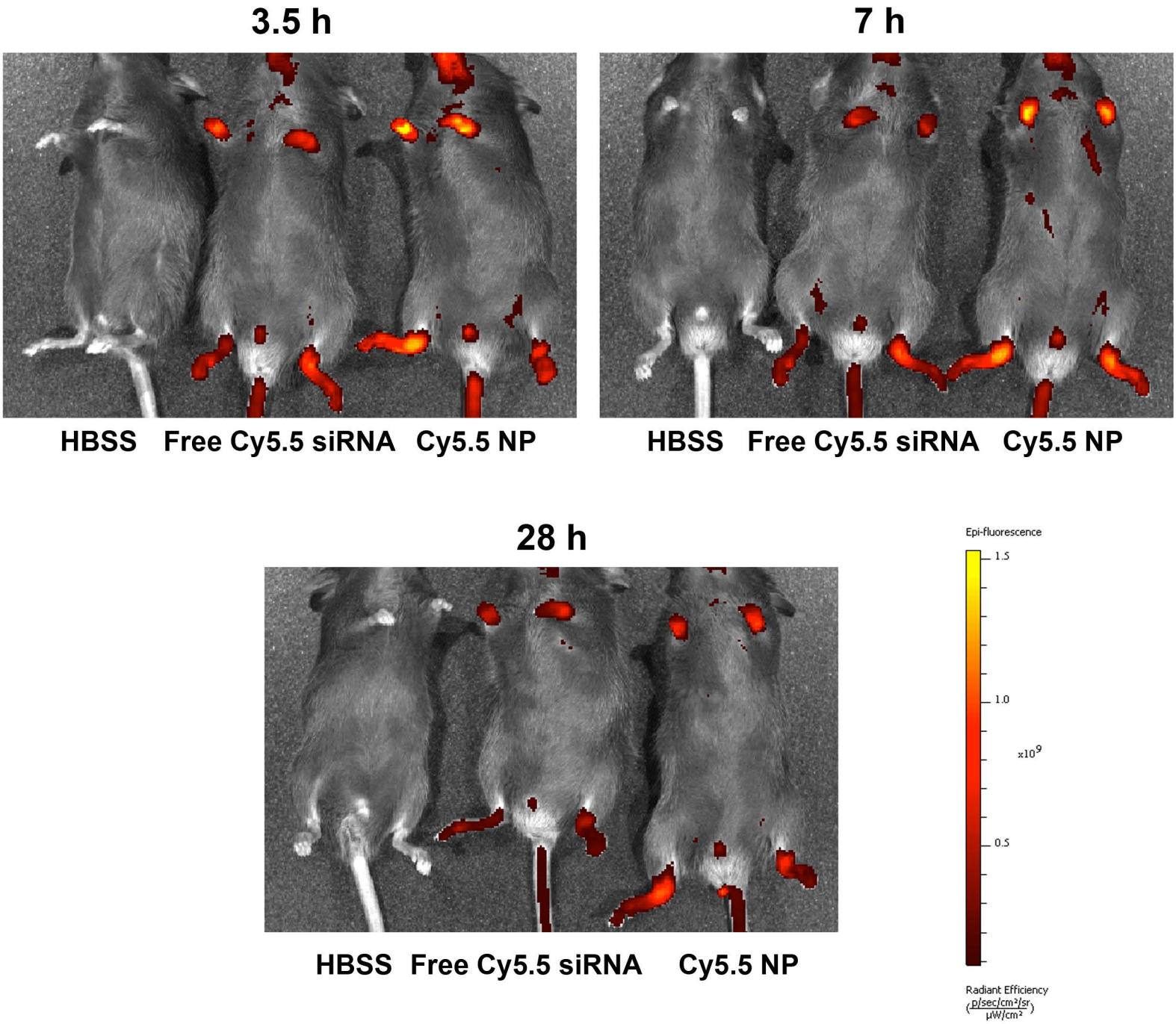

Figure S1. siRNA accumulation in inflamed paws
Day 4 arthritic mice received i.v. injection of HBSS, free Cy5.5-labeled scrambled siRNA (free Cy5.5 siRNA), or p5RHH-Cy5.5-labeled scrambled siRNA nanoparticles (Cy5.5 NP) and in vivo fluorescent images were acquired at 3.5 h, 7h, and 28 h post injection.

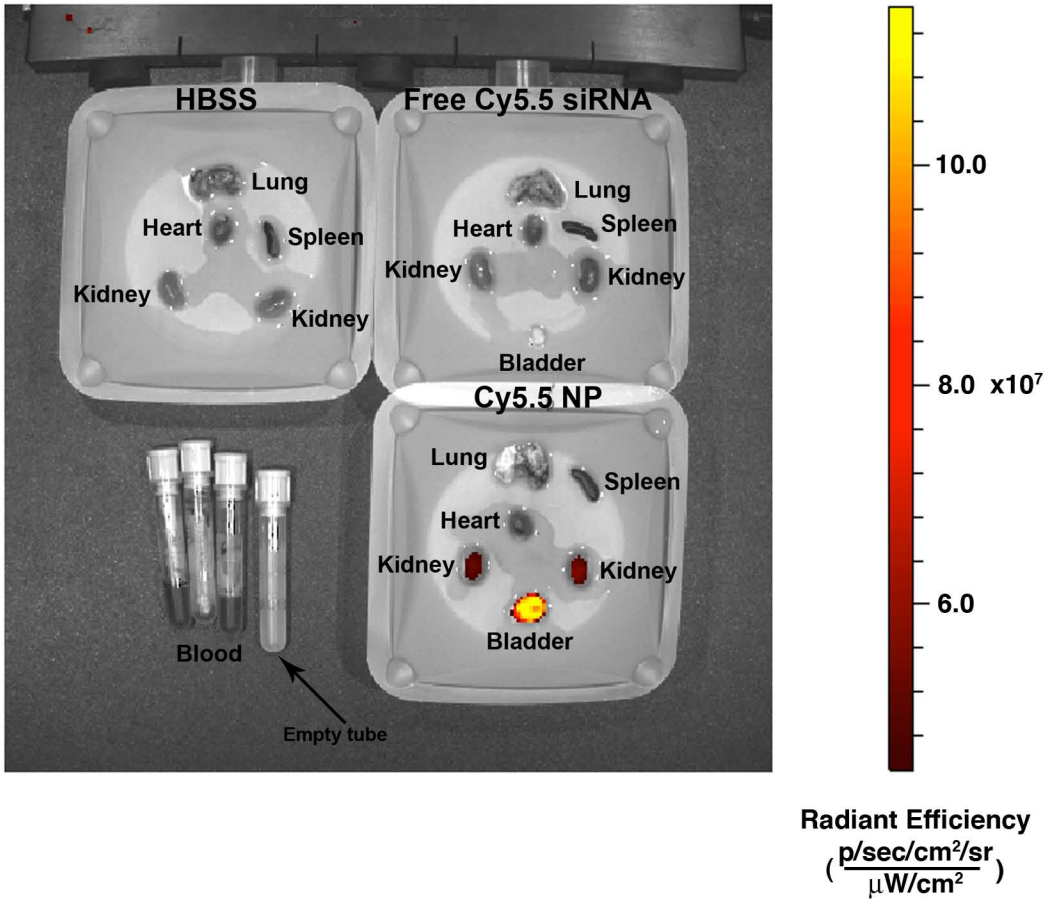

Figure S2. In vivo stability of p5RHH-siRNA nanoparticles
Mice were injected with HBSS, free Cy5.5-labeled scrambled siRNA (free Cy5.5 siRNA), or Cy5.5 NP. Organs and blood were collected 24 h after injection for fluorescence imaging.

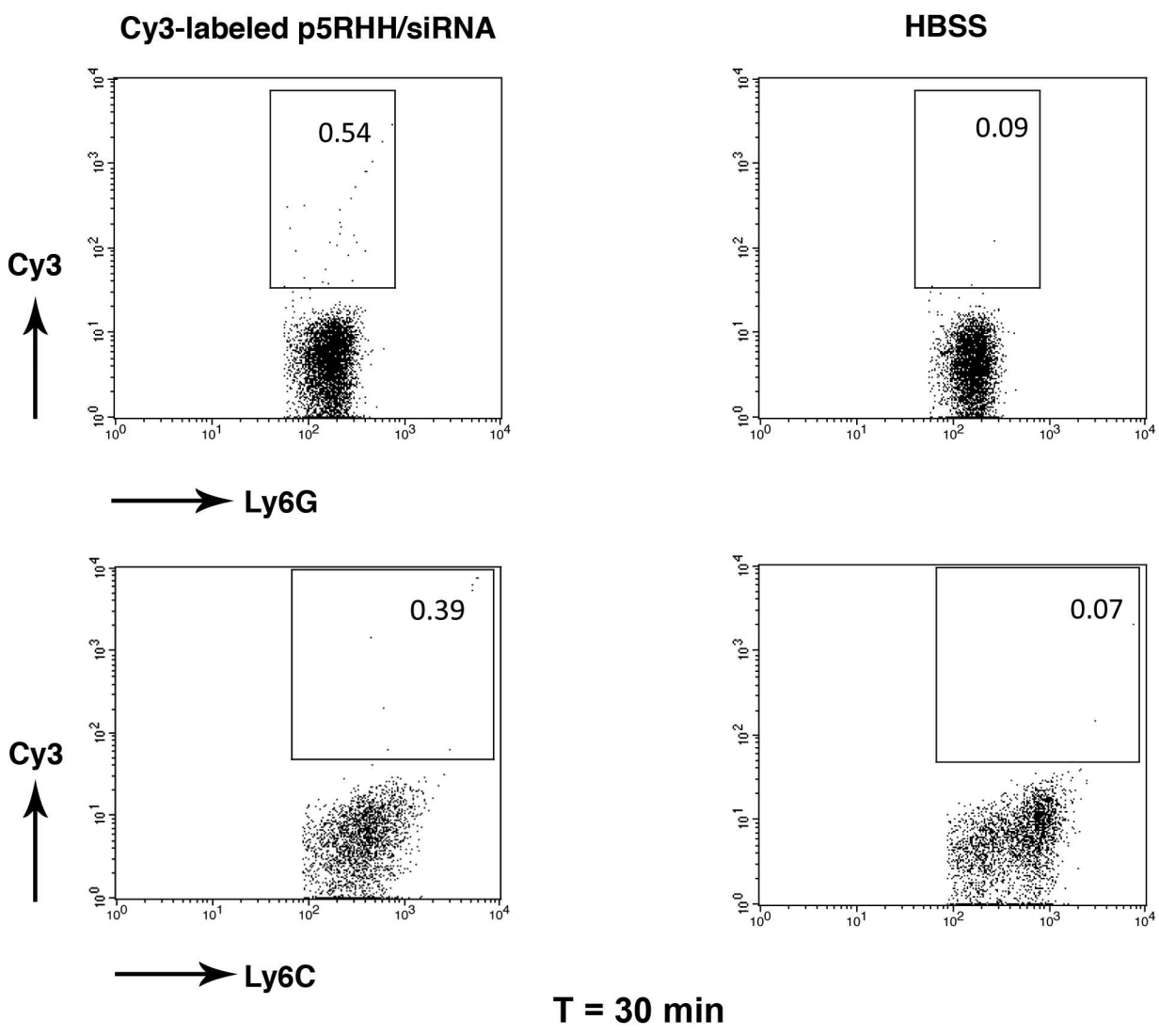

Figure S3. Minimal uptake of p5RHH/siRNA nanoparticles by circulating phagocytes
Mice were injected with HBSS or nanoparticles containing Cy3-labeled scrambled siRNA sequence. After 30 min mice were sacrificed and peripheral blood white cells were obtained and analyzed for cell-associated nanoparticles ($Cy3^+$ cells) by flow cytometry. Cells were co-stained with Ly6G (neutrophils) or Ly6C (monocytes). Percentage of double-positive cells ($Cy3^+/Ly6G^+$ or $Cy3^+/Ly6C^+$) is indicated in boxed areas.

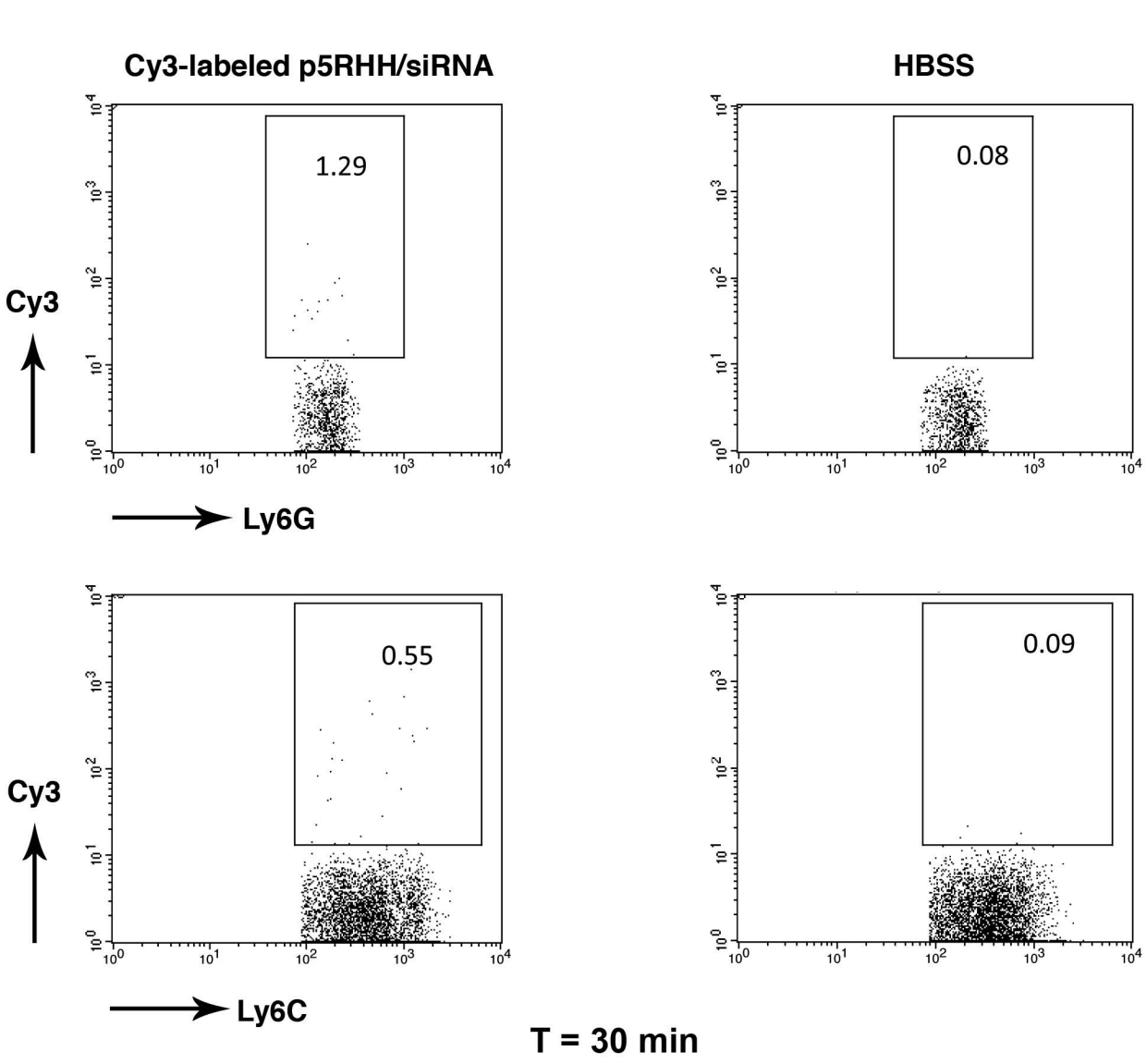

Figure S4. Minimal uptake of p5RHH/siRNA nanoparticles by splenocytes
Mice were injected with HBSS or nanoparticles containing Cy3-labeled scrambled siRNA sequence. After 30 min mice were sacrificed and splenocytes were obtained and analyzed for cell-associated nanoparticles ($Cy3^+$ cells) by flow cytometry. Cells were co-stained with Ly6G (neutrophils) and Ly6C (monocytes). Percentage of double-positive cells ($Cy3^+/Ly6G^+$ or $Cy3^+/Ly6C^+$) is indicated in boxed areas.

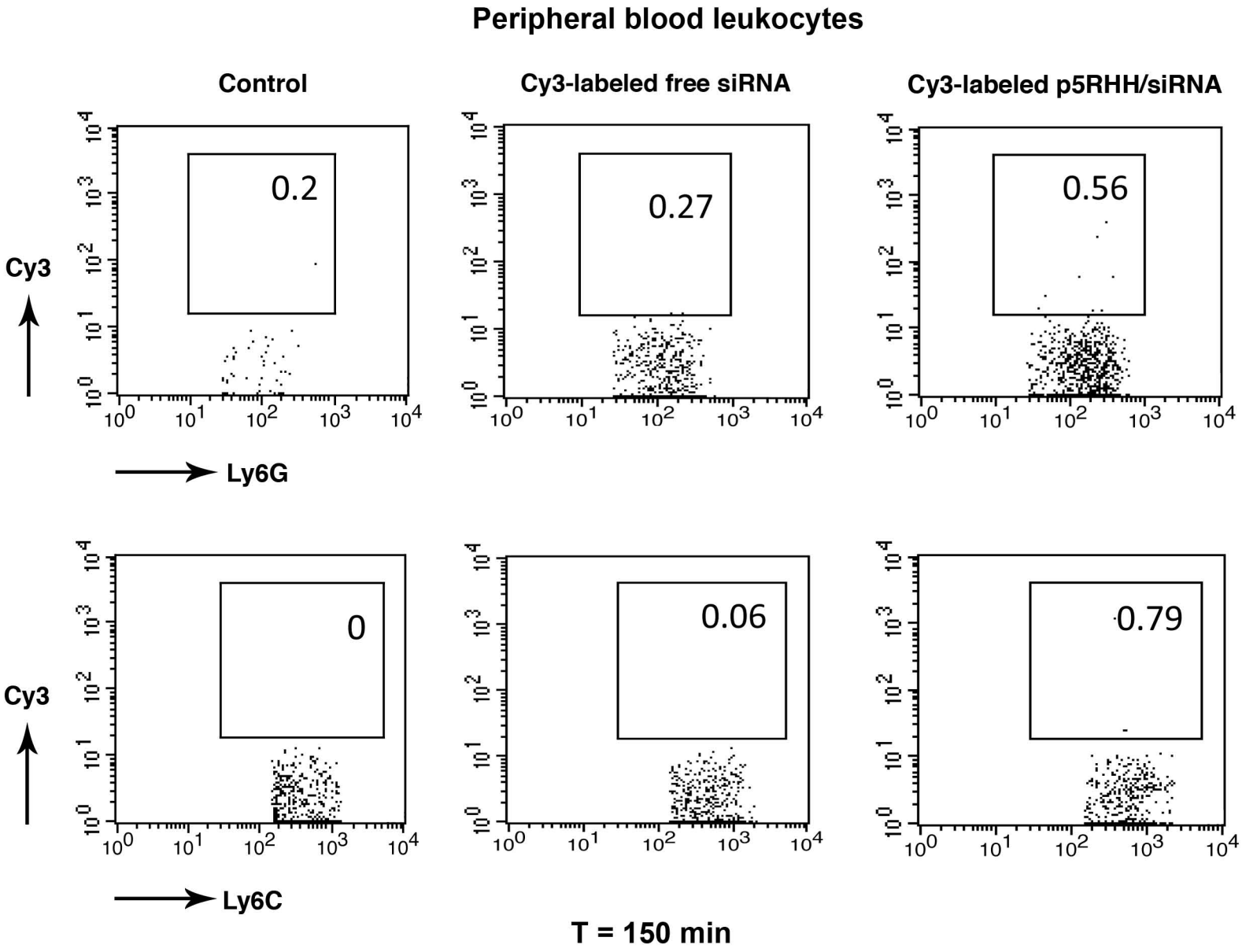

Figure S5. Minimal uptake of p5RHH/siRNA nanoparticles by circulating phagocytes
Mice were injected with nanoparticles containing Cy3-labeled p65 siRNA or free Cy3-labeled p65 siRNa. After 150 min mice were sacrificed and peripheral blood white cells were obtained and analyzed for cell-associated nanoparticles ($Cy3^+$ cells) by flow cytometry. Cells were co-stained with Ly6G (neutrophils) or Ly6C (monocytes). Percentage of double-positive cells ($Cy3^+/Ly6G^+$ or $Cy3^+/Ly6C^+$) is indicated in boxed areas. Uninjected mouse served as baseline control.

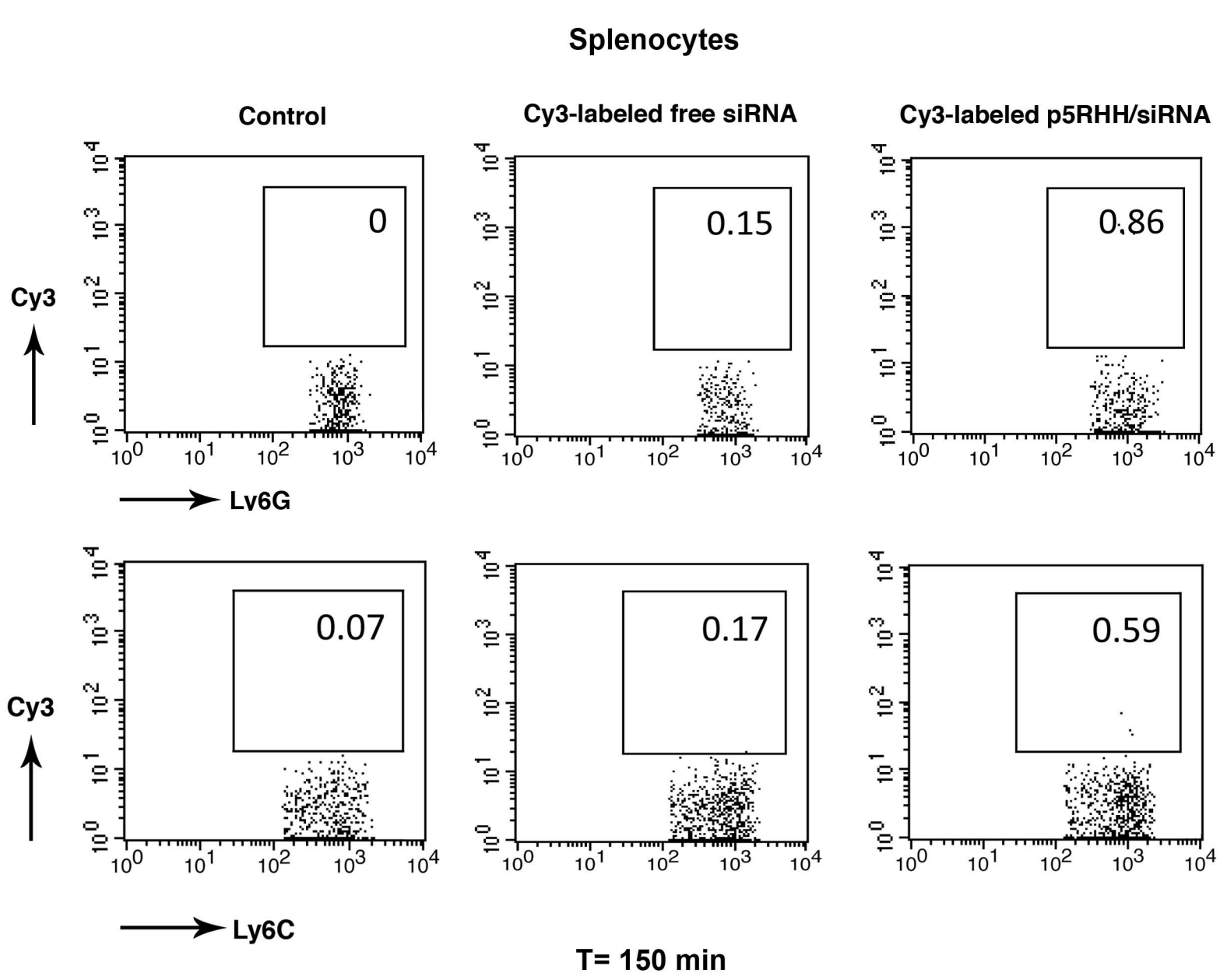

Figure S6. Minimal uptake of p5RHH/siRNA nanoparticles by splenocytes
Mice were injected with nanoparticles containing Cy3-labeled p65 siRNA. After 150 min mice were sacrificed and splenocytes were obtained and analyzed for cell-associated nanoparticles ($Cy3^+$ cells) by flow cytometry. Cells were co-stained with Ly6G (neutrophils) and Ly6C (monocytes). Percentage of double-positive cells ($Cy3^+/Ly6G^+$ or $Cy3^+/Ly6C^+$) is indicated in boxed areas. $TCR\beta^+$ (T) and $CD19^+$ (B) cells had no Cy3-associated signal. Uninjected mouse served as baseline control.

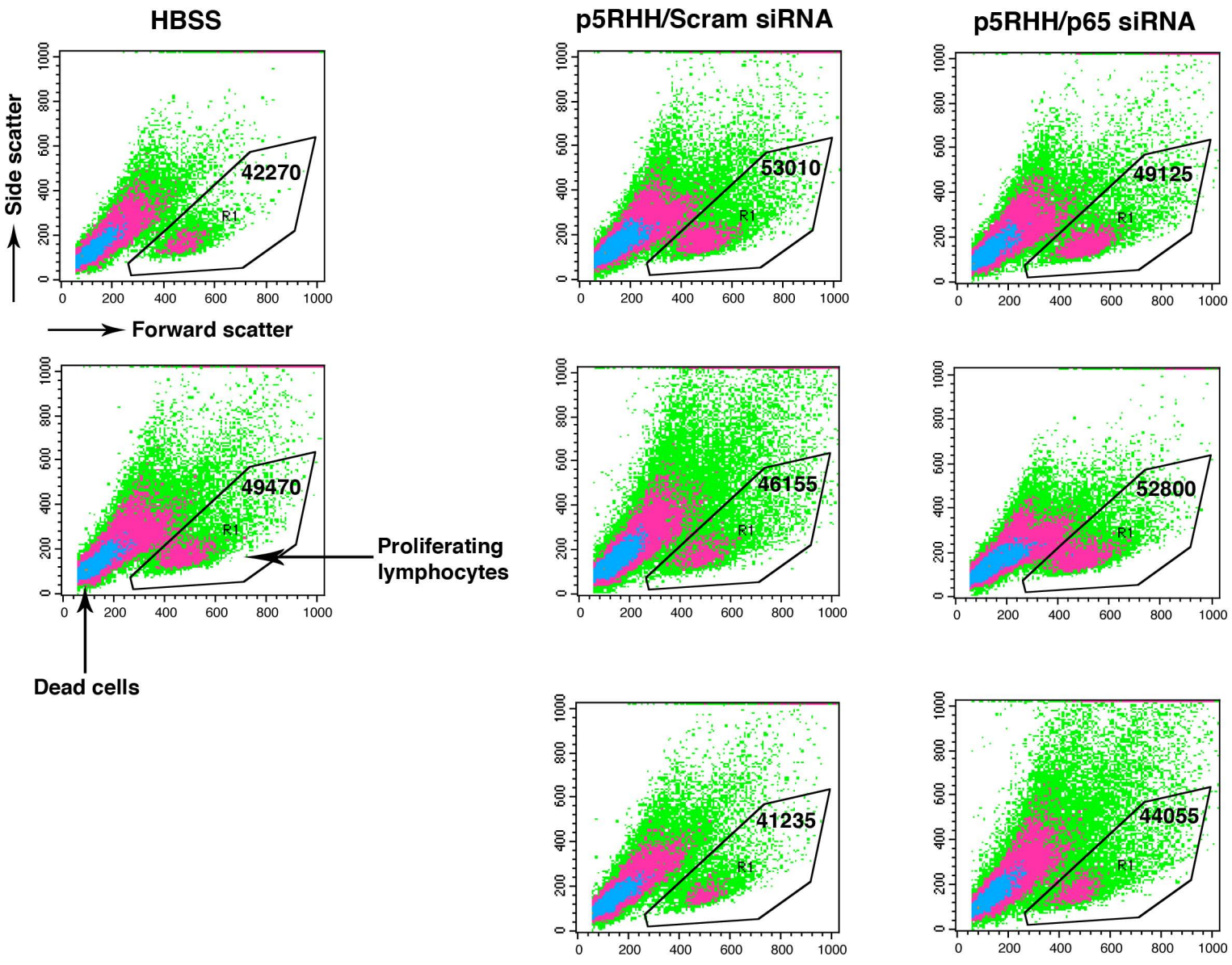

Figure S7. Ex vivo CD4⁺ T cell proliferation

On day 10 spleens were harvested and $CD4^+$ T cells were purified by positive magnetic bead sorting according to manufacturer's protocol (Myltenyi Biotec Inc.). T cells (2×10^5) were plated in triplicates in 96-well plates coated with anti-CD3 monoclonal antibody (5 ug/ml). After 72 h cells were harvested and enumerated by flow cytometry against time (45 sec). The number (events) of proliferating T cells in gated area is indicated.