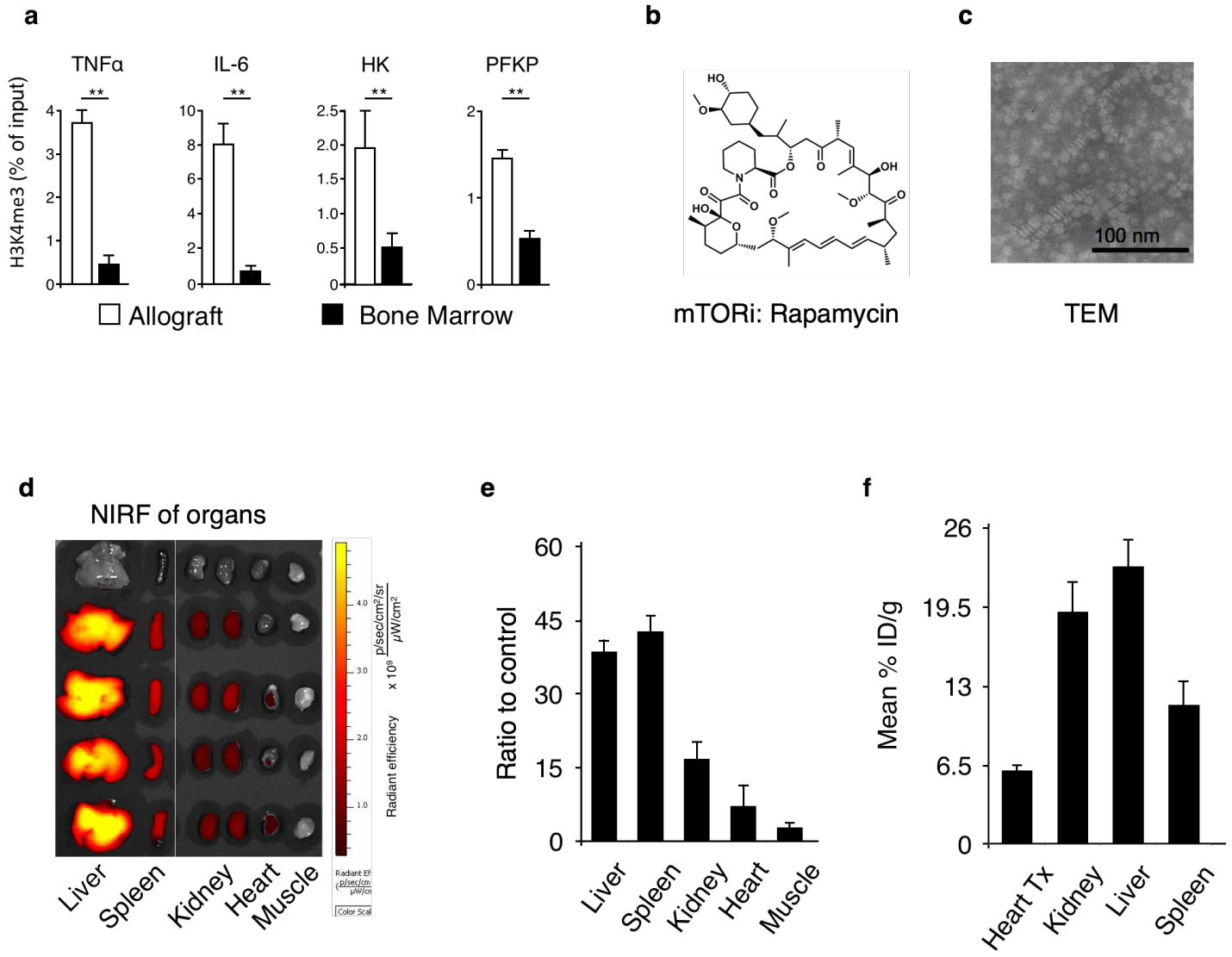

Figure S1. Related to Figures 1, 2 and 3. Development and in vivo distribution of mTORi-HDL. **(A)** Chromatin immunoprecipitation assay (ChIP) of graft-infiltrating and bone marrow monocytes from untreated rejecting recipients at day 6 post-transplantation. ChIP was performed to evaluate histone H3K4 trimethylation. Abundance of four trained immunity-related genes was examined by qPCR (n=3, Wilcoxon signed rank test, ** P<0.01. Results from 1 experiment). **(B)** Chemical structure of the mTOR inhibitor (mTORi) rapamycin. **(C)** Transmission electron micrograph showing the discoidal morphology of mTORi-HDL nanobiologic. **(D)** mTORi-HDL's biodistribution in C57/Bl6 wild type mice. Representative near infrared fluorescence images (NIRF) of organs injected with either PBS control (first row of organs) or DiR-labeled mTORi-HDL showing accumulation in liver, spleen, lung, kidney, heart and muscle. **(E)** Bars represent the control to mTORi-HDL-DiR accumulation ratio in each organ, calculated by dividing the total signal of each organ in the control and mTORi-HDL-DiR groups (n=4 mice/group. Results from 3 experiments). **(F)** PET-quantified uptake values according to the mean % ID/g in transplanted heart, kidney, liver and spleen (n=3 mice. Results from 3 experiments).

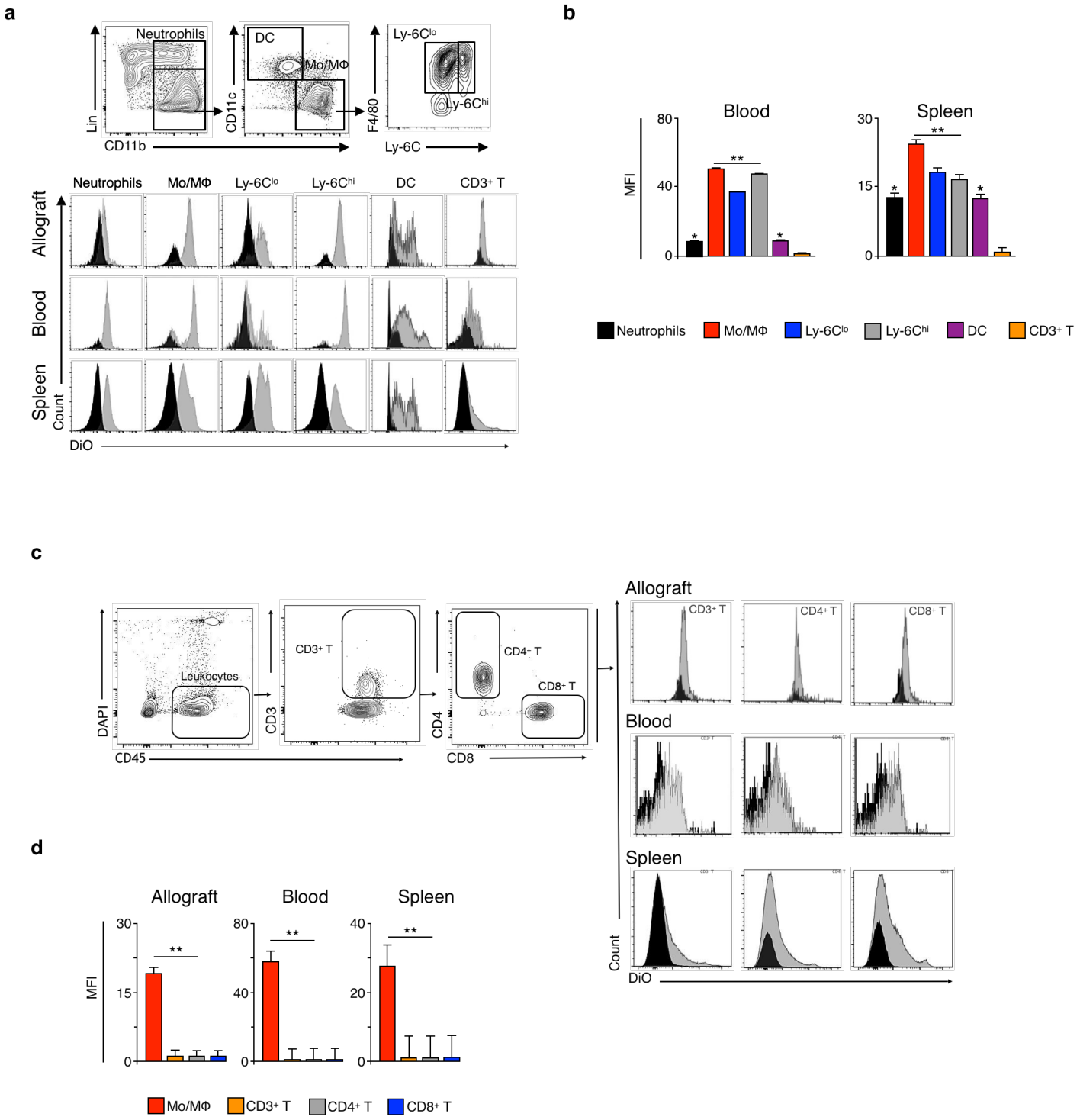

Figure S2. Related to Figures 2 and 3. In vivo cellular targeting of mTORi-HDL. **(A)** Flow cytometry gating strategy to distinguish myeloid cells in blood, spleen and the transplanted heart. Grey histograms show immune cell distribution in the mice injected with DiO-labeled mTORi-HDL compared to control (black histogram). **(B)** Mean fluorescence intensity (MFI) of neutrophils, monocytes/macrophages, Ly-6C^{lo} and Ly-6C^{hi} monocytes/macrophages, dendritic cells and T cells in the blood and spleen (n=4 mice/group, one-way ANOVA, *P<0.05; **P<0.01. Results from 3 experiments). **(C)** Flow cytometry gating strategy to distinguish T cells in blood, spleen and the transplanted heart. Grey histograms (right) show the T cell distribution in mice injected with DiO-labeled mTORi-HDL compared to distribution in control animals (black histogram). **(D)** Mean fluorescence intensity (MFI) of monocytes/macrophages, CD3+ T, CD4+ T and CD8+ T cells in blood and the transplanted heart (n= 4 mice/group, one-way ANOVA, **P<0.01. Results from 3 experiments).

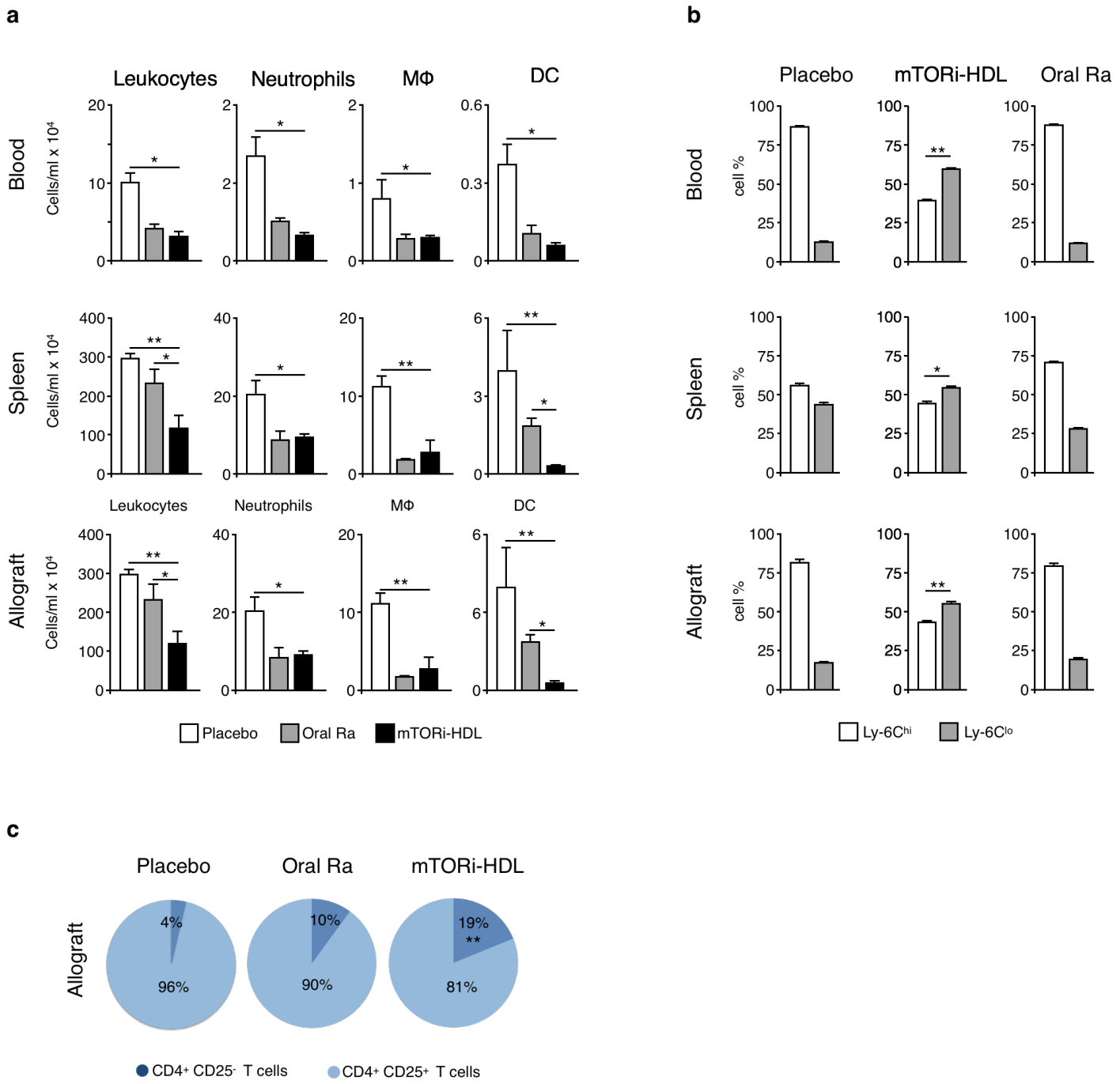

Figure S3. Related to Figures 3 and 4. mTORi-HDL rebalances the myeloid and Treg compartment in vivo. **(A)** Flow cytometric analysis of cell suspensions retrieved from allograft, blood and spleen of placebo, oral rapamycin (5mg/kg) and mTORi-HDL-treated (5mg/kg) allograft recipients at day 6 post transplantation. Total numbers of leukocytes, neutrophils, macrophages (MΦ) and dendritic cells (DC) are shown (n=4 mice/group, one-way ANOVA, *P<0.05; **P<0.01. Results from 3 experiments). **(B)** Ratio of Ly-6C^{hi} to Ly-6C^{lo} monocytes in the blood, spleen and heart allograft from placebo, oral rapamycin (5mg/kg) and mTORi-HDL-treated (5mg/kg) allograft recipients (n=4 per group, one-way ANOVA, *P<0.05; **P<0.01. Results from 3 experiments). **(C)** Percentage of graft-infiltrating CD4^{+}CD25^{+} vs. CD4^{+}CD25^{-} T-cells from placebo, oral rapamycin (5mg/kg) and mTORi-HDL-treated (5mg/kg) allograft recipients (n=4 mice/group, one-Way ANOVA, **P<0.01. Results from 3 experiments).

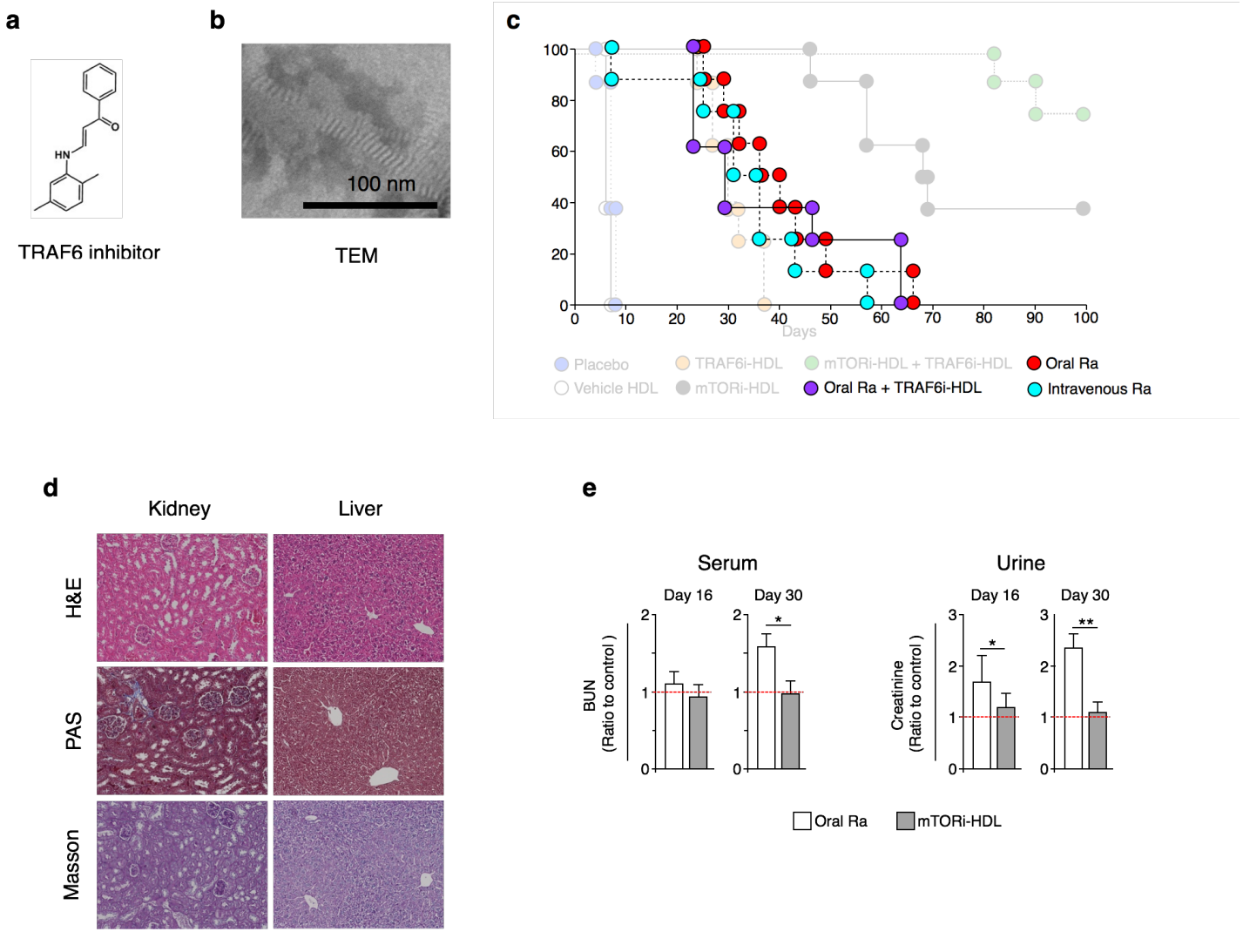

Figure S4. Related to Figure 4. Therapeutic effects of combined mTORi-HDL and TRAF6i-HDL nanobiologics. TRAF6i-HDL nanobiologic. **(A)** Chemical structure of the TRAF6 inhibitor. **(B)** Transmission electron micrograph showing the discoidal morphology of TRAF6i-HDL. The nanoparticles had a mean hydrodynamic radius of 19.2 ± 3.1 nm and a drug incorporation efficiency of 84.6 ± 8.6%, as determined by DLS and HPLC, respectively. **(C)** Graft survival curves of oral rapamycin, Intravenous rapamycin and oral rapamycin + TRAF6i-HDL (n=8 mice in each group). The background shows graft survival curves for placebo, HDL vehicle, TRAF6i-HDL, mTORi-HDL and mTORi-HDL/TRAF6i-HDL combination therapy form Figure 3g. **(D)** Representative kidney and liver immunohistochemical images for hematoxylin/eosin (H&E), Periodic Acid Schiff (PAS) and Masson Trichrome from mTORi/TRAF6i-HDL-treated transplant recipients collected at day 100 after transplantation. Kidney shows no significant changes in the three compartments of kidney parenchyma. Glomeruli appear normal, with no evidence of glomerulosclerosis. The tubules show no significant atrophy or any evidence of epithelial cell injury including vacuolization, loss of brush border or mitosis. Liver has normal acinar and lobular architecture. There is no evidence of inflammation or fibrosis in the portal tract and hepatic parenchyma. Hepatocytes are normal with no evidence of cholestasis, inclusions or apoptosis (n=4 mice; magnification X200). **(E)** Toxicity associated with mTORi-HDL treatment. Recipient mice received either the mTORi-HDL treatment regimen (5mg/kg on days 0 2, and 5 post-transplantation) or an oral rapamycin a treatment dose (5mg/kg every day for 15 days) to achieve the same therapeutic outcome (100% allograft survival for 30 days). mTORi-HDL has no significant effects on blood urea nitrogen (BUN) or serum creatinine, but kidney toxicity parameters show statistical differences between oral rapamycin and mTORi-HDL. No differences between syngeneic and mTORi-HDL recipients were observed (n=4 mice/group, one-way ANOVA, *P<0.05; **P<0.01. Results from 3 experiments).