Supplemental Figure 1: Dose response study of mTOR pathway inhibition by FC-rapa and unconjugated rapamycin in KB cells. KB cells were incubated for 5 hours with the indicated concentrations of FC-rapa or unconjugated rapamycin prior to immunostaining with P-S6 (Ser235/6) antibodies followed by immunofluorescent detection (green).

Supplemental Figure 2: Inhibition of mTOR pathway activity is dependent on FR expression. Pretreatment of KB cells with excess folate prevents FC-rapa, but not unconjugated rapamycin, from inhibiting mTOR pathway activity as assessed by immunofluorescence microscopy using a P-S6 (Ser235/6) antibody (green). Nuclear stain (DAPI) in blue.

Supplemental Figure 3: FC-rapa treatment of *bpk* mice preferentially inhibits growth of distal tubule/collecting duct-derived cysts. Renal sections derived from non-treated and FC-rapa-treated *bpk* mutant animals were subjected to staining with fluorescent-labeled lectins LTL (green) and DBA (red) which label proximal and distal tubules/collecting ducts, respectively. A, quantification; B, representative fluorescence micrographs PT, proximal tubule; DT, distal tubule; CD, collecting duct.

Supplemental Figure 4: High-dose FC-rapa has systemic effects in young, growing mice. (A) Growth curve shows inhibition of body weight gain; The thymus (B) and spleen (C) weights are disproportionally affected by FC-rapa treatment suggesting immunosuppression; (D) inhibition of mTOR pathway activity in off-target tissues.

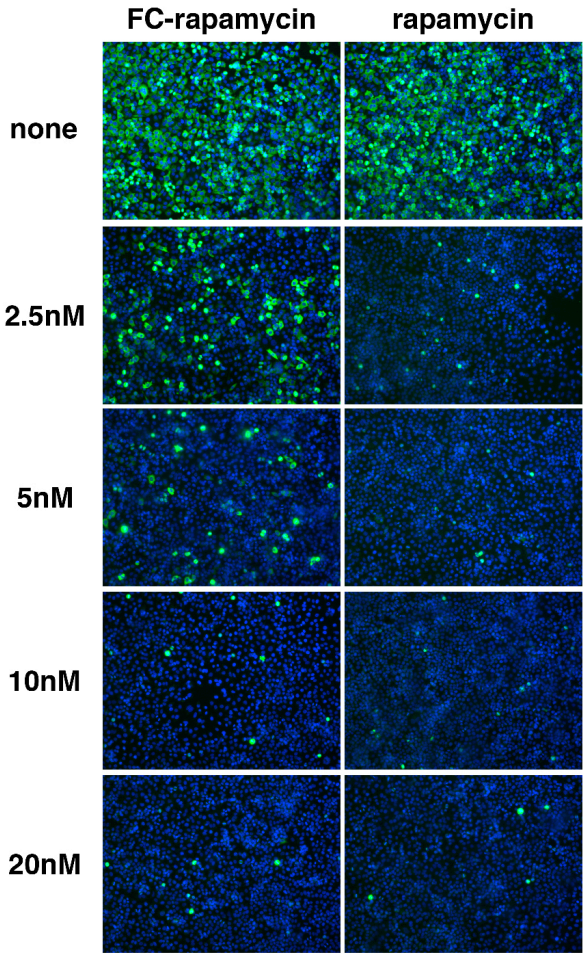
Supplemental Figure 5: Acute LPS treatment induces mTOR pathway activation in numerous tissues. Adult wild-type mice were treated for two hours with the indicated doses of LPS prior to sacrifice and analysis of mTOR activity by western blot analysis. Note that an LPS dose of 25mg/kg robustly stimulated mTOR pathway activity in the kidney, spleen, thymus, and lung as measured by the surrogate marker P-S6 (S235/6).

Supplemental Figure 6: Low-dose FC-rapa lacks systemic effects. Treatment of young wild-type mice (day 7 – 21) with low dose (0.3 μmol/kg/day) FC-rapa had no significant effect on body weight gain (A) or thymus weight (B) compared to mice treated with low dose (0.3 μmol/kg/day) unconjugated rapamycin.

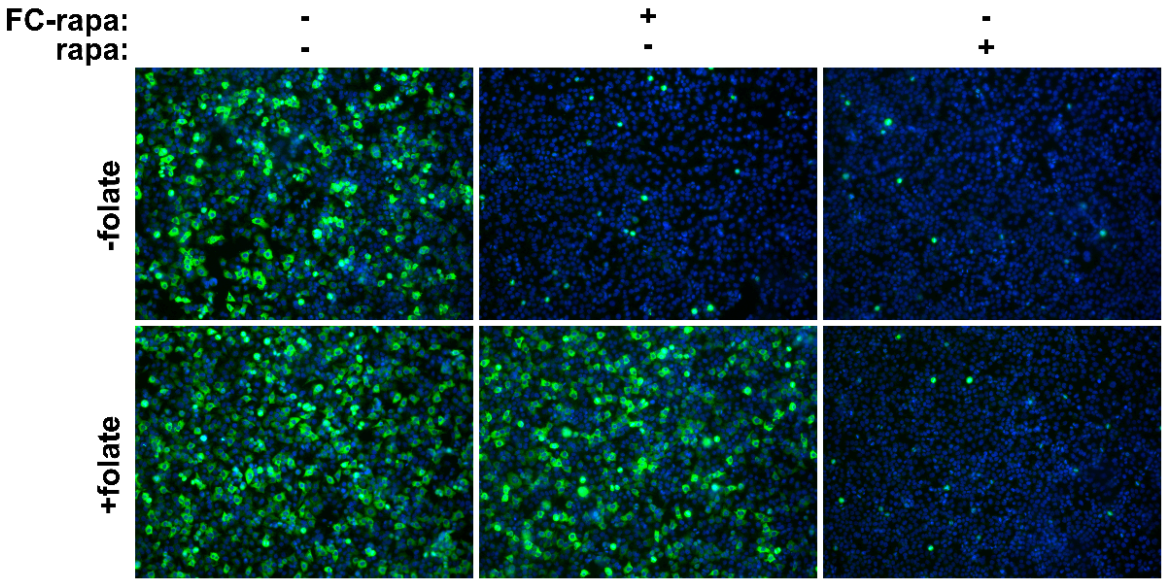
Supplemental Table 1: Folate receptor expression is retained in renal cysts. Standard paraffin sections were subjected to immunostaining using a monoclonal antibody against human FRα (mAb-343/3D2; Endocyte, Inc.) or an affinity-purified, rabbit polyclonal antibody raised against bovine milk folate binding protein (PU-17; Endocyte, Inc.). A common scoring system was used, where 0 is the staining equivalent to background (relative to isotype-stained controls), and 3+ is the most intensive staining. Human serous ovarian cancer (OVCA) specimens served as a positive control. The percentage of all cells that stained in the field of view is listed at each of the 4 levels of intensity.

Tissue	Specimen Number	IHC Score
Human Control Kidney	1	3+
	2	3+
Human ADPKD	1	3+
	2	2+
	3	2+
Human Serous Ovarian Cancer	1	2+
	2	3+
Mouse Control Kidney	1	1+
	2	2+
	3	2+
ORPK-Rescue Mouse Kidney	1	3+
Bpk Mouse Kidney	1	2+
	2	2+

Supplemental Table 1



Supplemental Fig. 1



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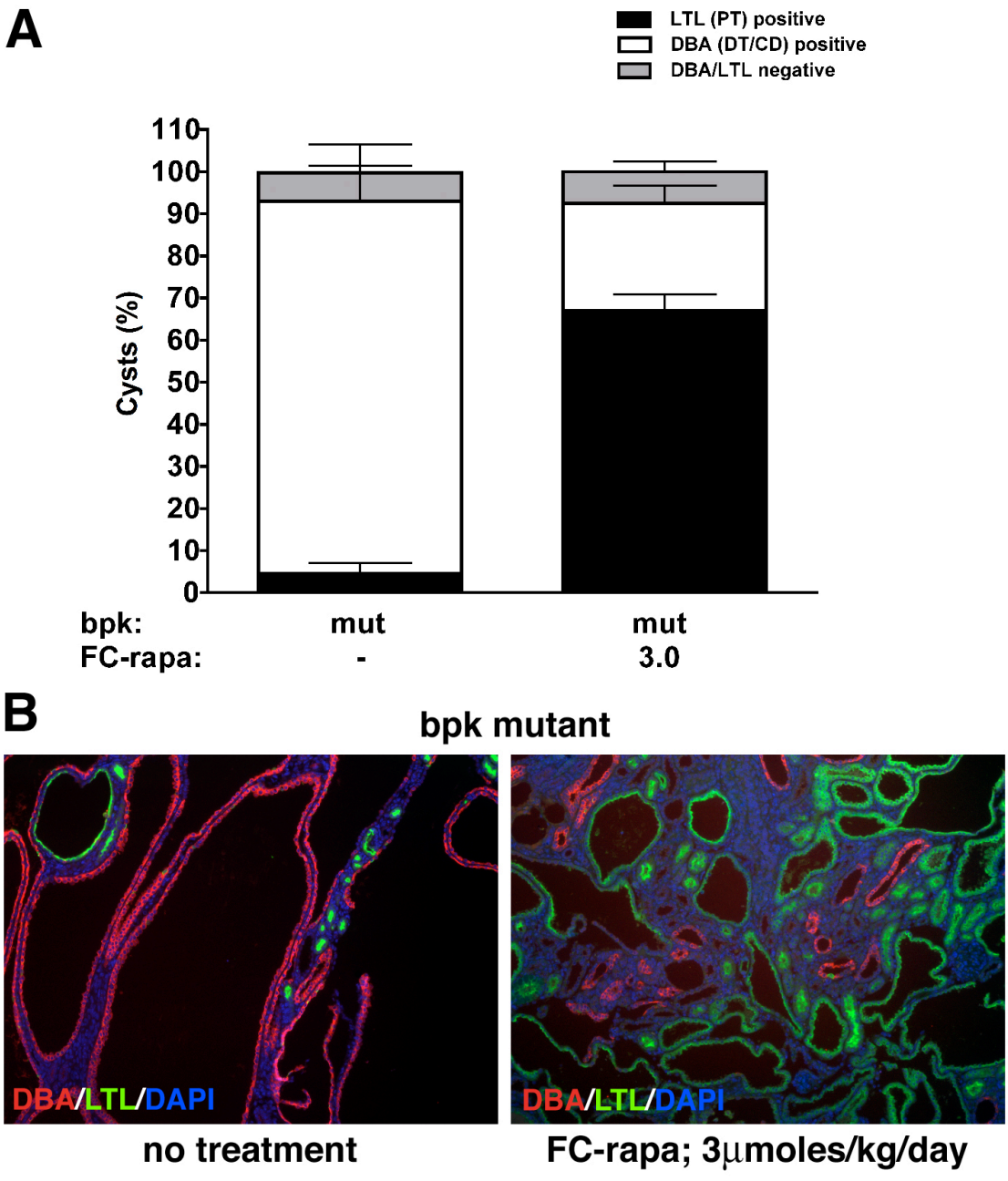

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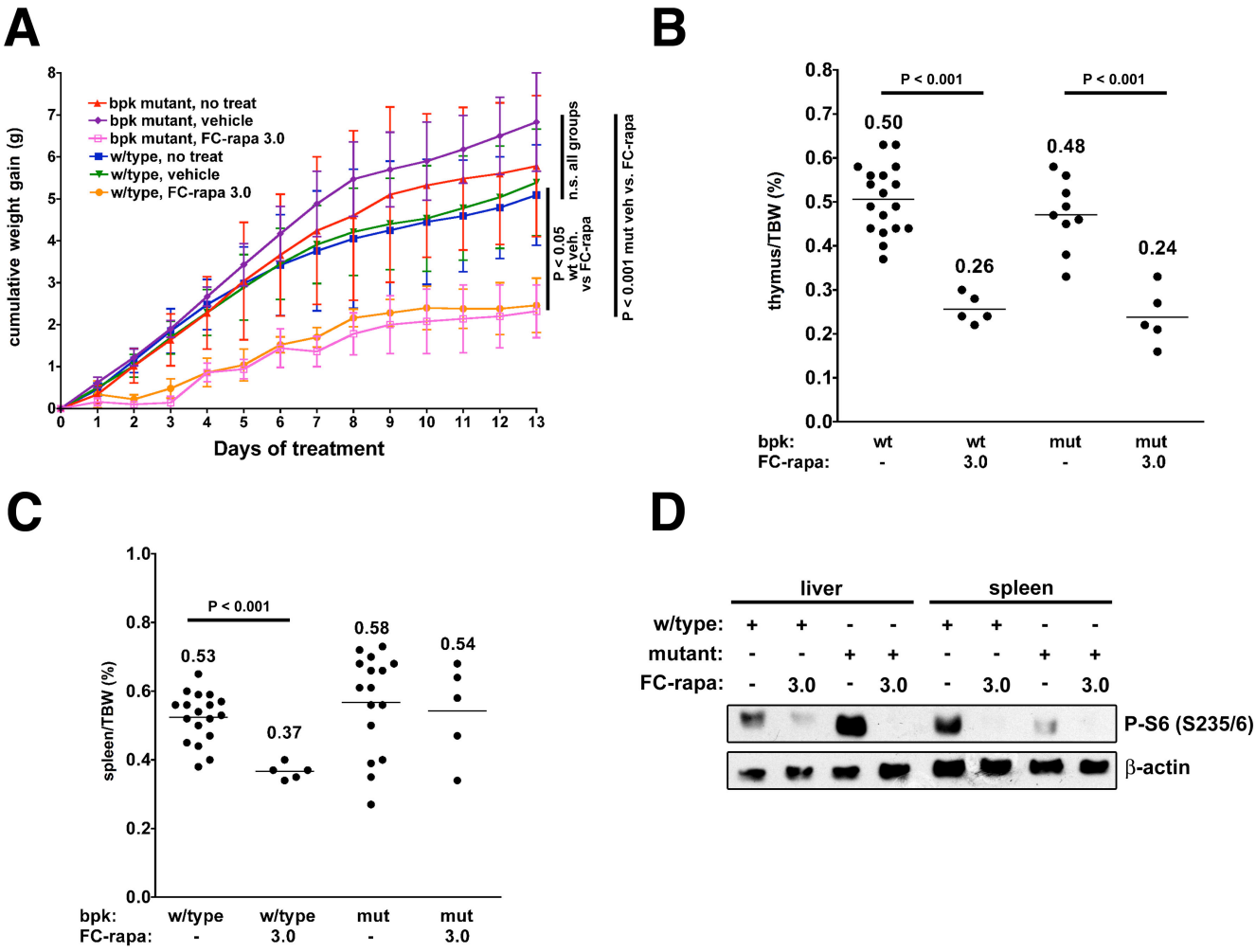

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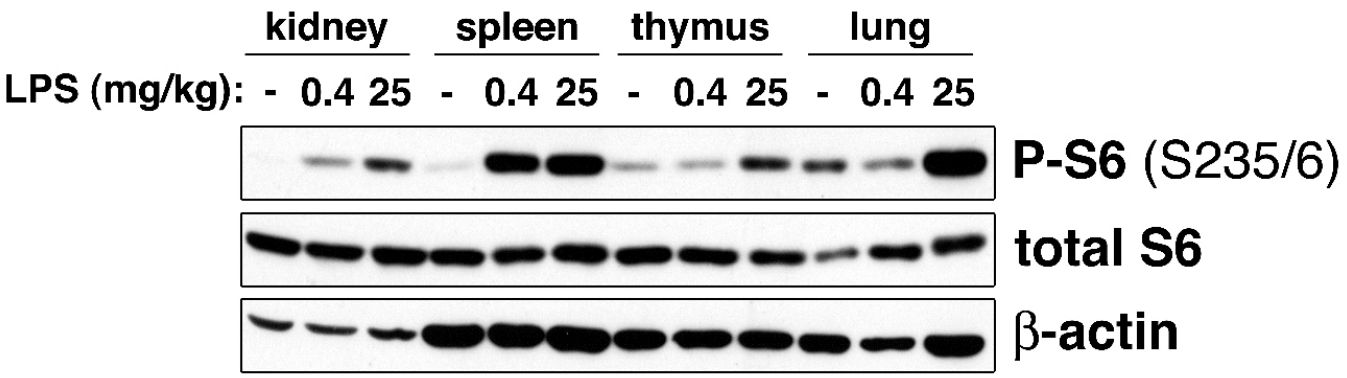
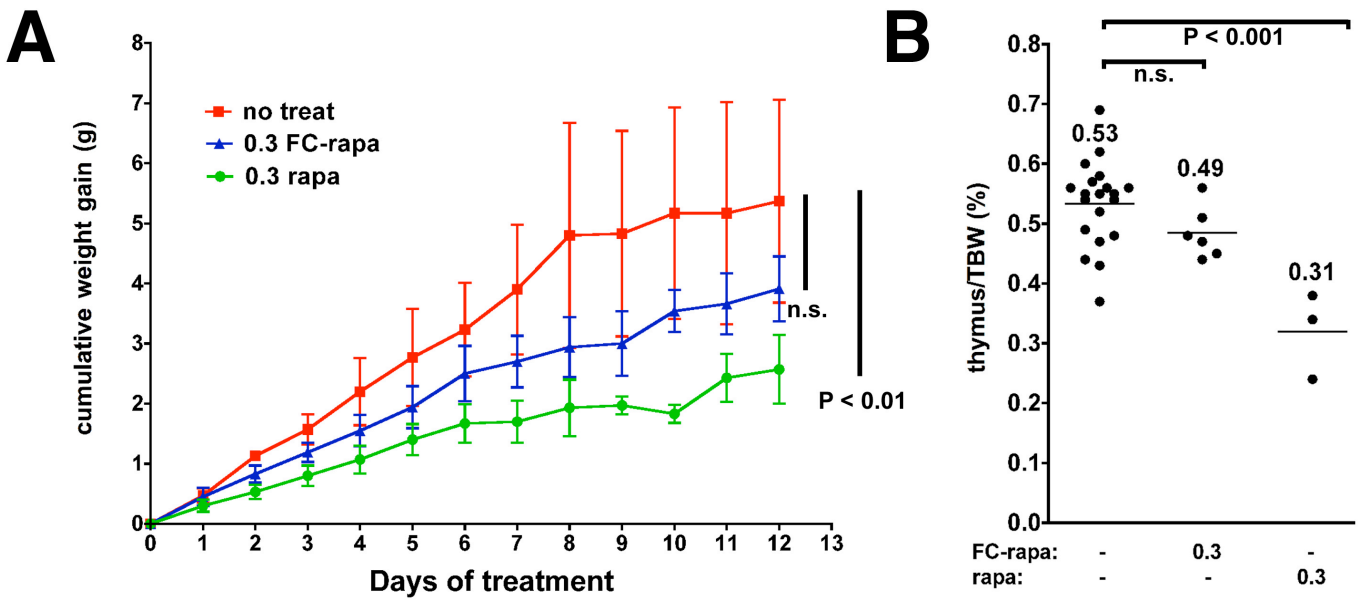


Supplemental Fig. 5



Supplemental Fig. 6