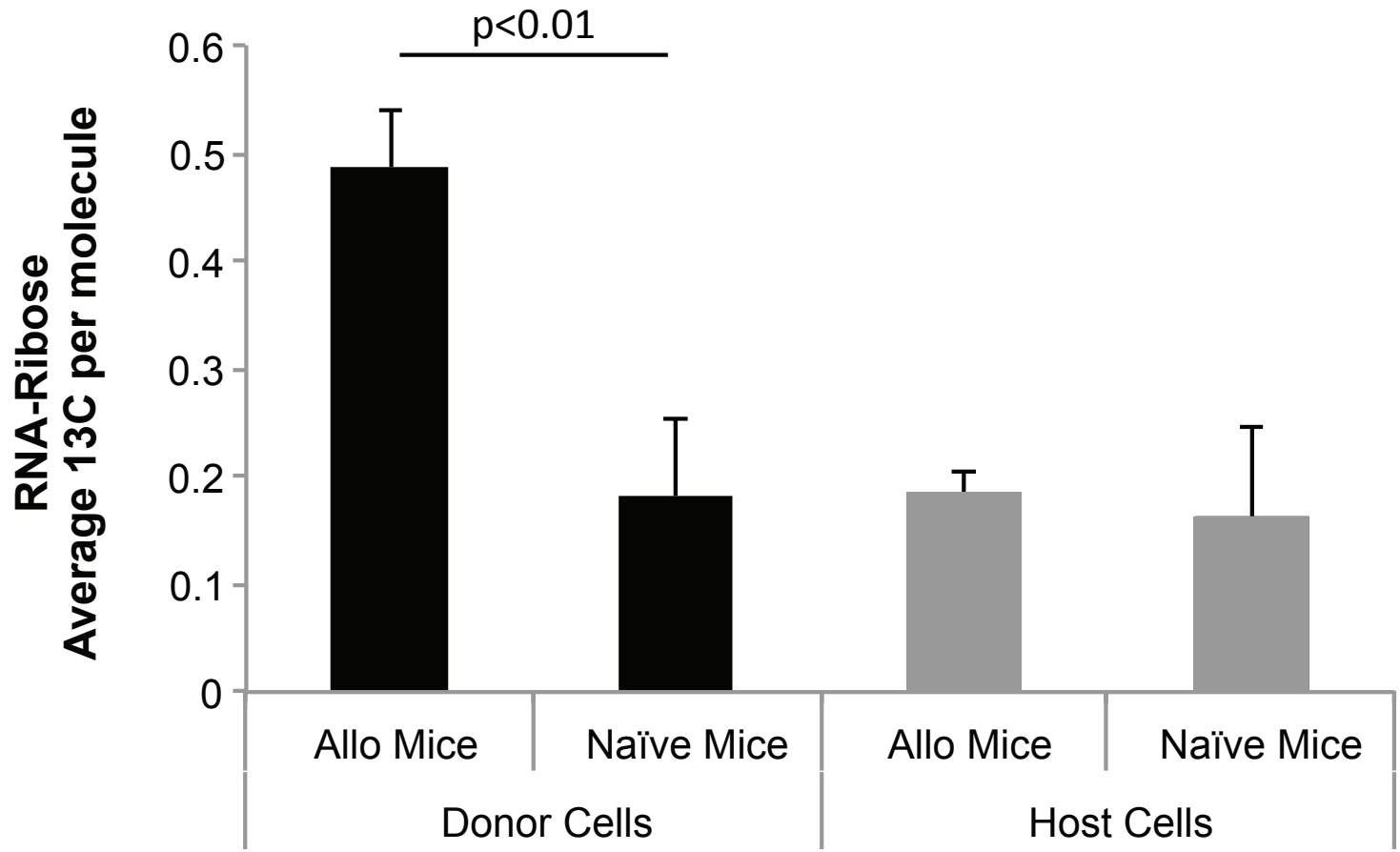
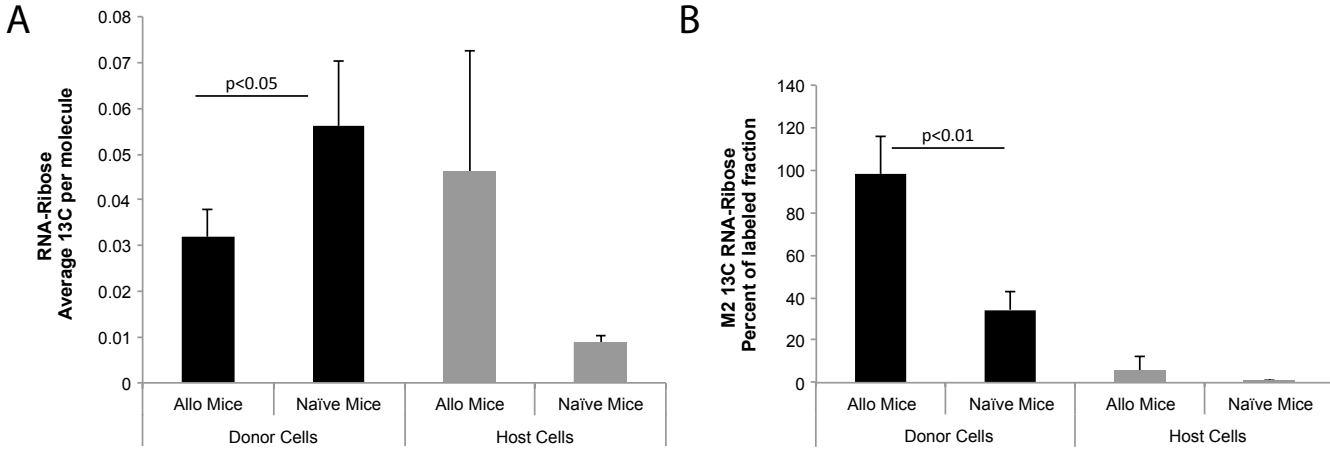
Supplemental Figure 1



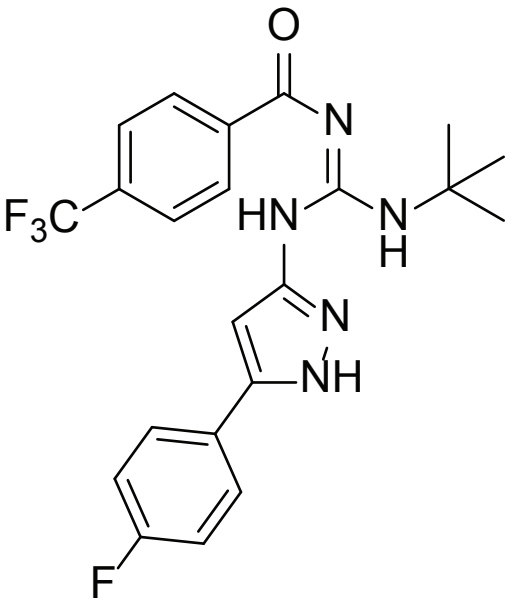
Redistribution of 13C from [U-13C5]-L-glutamine into RNA-ribose. Indicated populations of T cells were isolated from B6→B6D2 F1 7 d after transplant (n=4 mice) and control mice (n=4 mice per group) 1 h after [U-13C5]-L-glutamine tracer was administered by IP injection. 13C content in RNA-ribose C1-C4 (m/z 242) is expressed.

Supplemental Figure 2



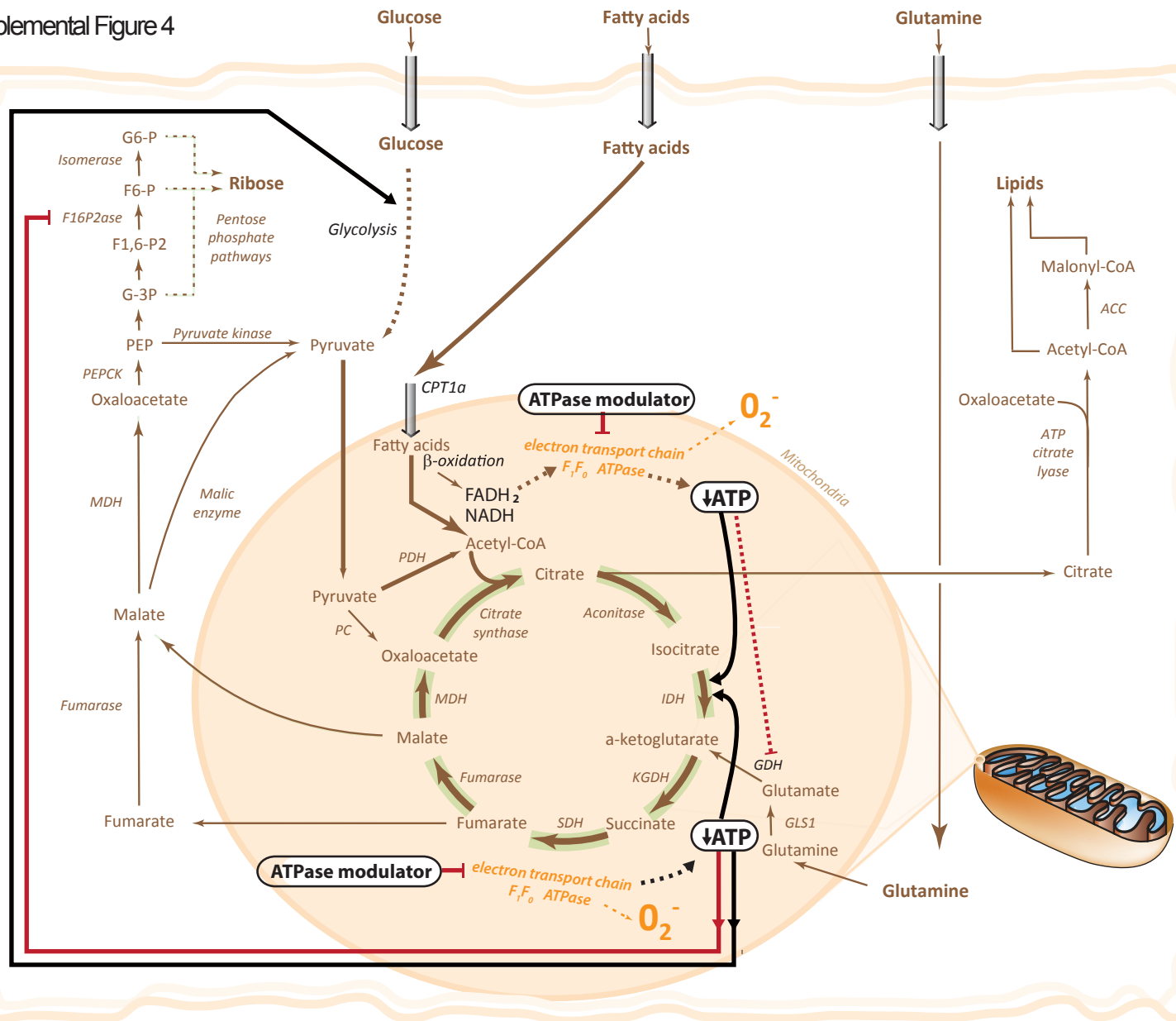
Redistribution of 13C from [U-13C16]-palmitate into RNA-ribose. A. Indicated populations of T cells were isolated from B6→B6D2 F1 7 d after transplant (n=4 mice) and control mice (n=4 mice per group) 3 h after [U-13C16]-palmitate tracer was administered by oral gavage. 13C content in RNA-ribose C1-C4 (m/z 242) was measured and is shown as mean ± standard deviation. B. Percent of total 13C-labeled ribose represented by m2 ribose isotopmer measured in RNA-ribose isolated from T cell populations after transplant as described in Supplemental Figure 1.

Supplemental Figure 3



Structure of LYC-31138

Supplemental Figure 4



Metabolic response to negative allosteric modulation of the ATPase. Negative modulation of the ATPase increases superoxide, diminishes anaplerosis and increases cycling TCA metabolism. Metabolic pathways are shown in brown with relative activity indicated by the weight of the line. Positive regulation is shown black lines and negative regulation as red lines. Dashed lines indicate multi-step processes. Green overlay highlights cyclic TCA activity. Abbreviations as in the legend of Figure 6.

Supplemental Table 1: Lactate production by T cells.

Treatment	Samples analyzed	Lactate production: nMol/min*10^6 cells (Std. Dev)
Unstimulated T cells	12	0.12 (0.07)
CD3/CD28 stimulated T cells (48 h)	9	3.41 (1.93)
Allo-reactive T cells (Day 5)	3	0.18 (0.07)
Allo-reactive T cells (Day 7)	5	0.53 (0.15)
Allo-reactive T cells (Day 14)	3	0.23 (0.09)

Supplemental Table 2: Pharmacologic Properties of LYC-31138 and reference compound Bz-423. Improved absorption after oral dosing and slower rate of clearance result in increased exposure ($AUC_{0\text{-}24h}$) to LYC-31138 compared to Bz-423.

	IC50 (inhibition of bovine ATP synthase)	Dose group (mice)	Clearance (mL/min/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (h*ng/mL)	F (%)
LYC-31138	2.72 uM	5 mg/Kg IV	2.47	6.09	NA	32433	NA
		15 mg/Kg PO	NA	6.53	1553	16634	17
Bz-423	3.24 uM	3 mg/Kg IV	26	4	3740	1930	NA