

**Table S1. Ucp1 mRNA levels**

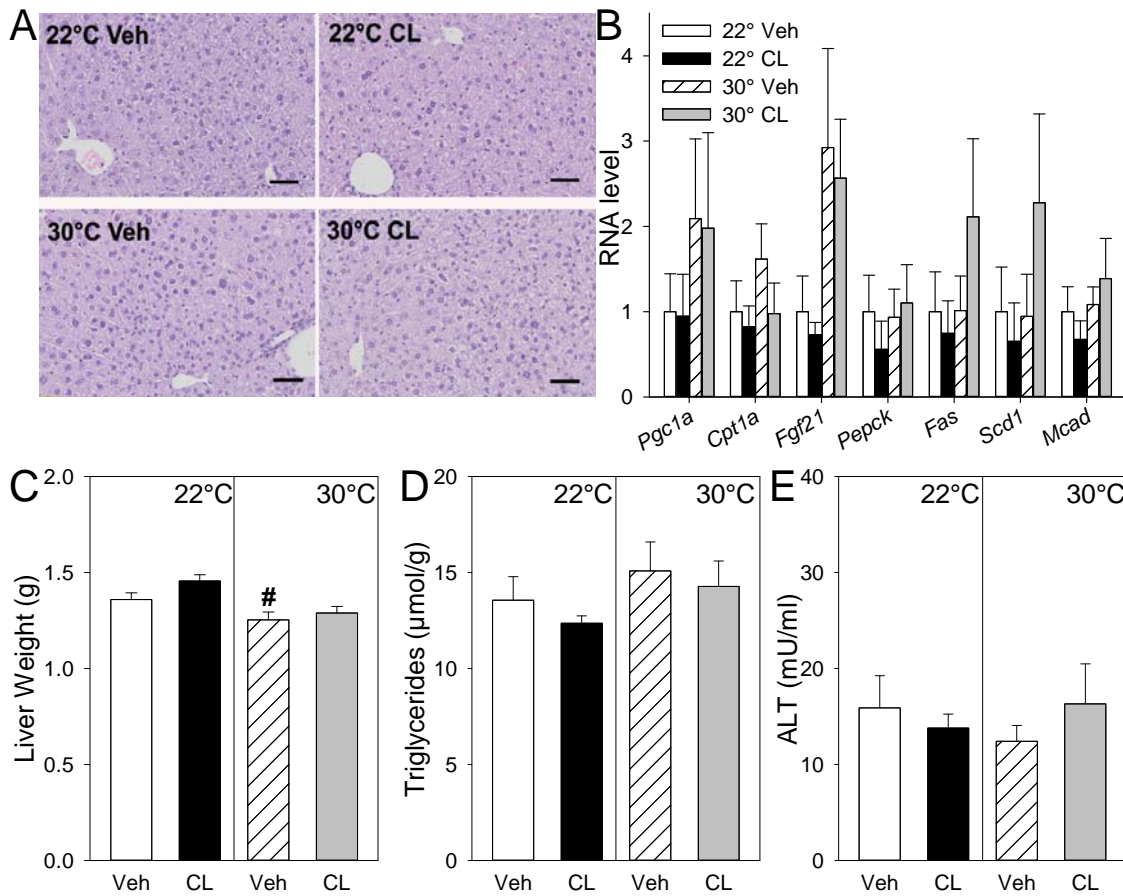
	<b>Chow</b>			<b>HFD</b>		
	<b>BAT</b>	<b>iWAT</b>	<b>eWAT</b>	<b>BAT</b>	<b>iWAT</b>	<b>eWAT</b>
<b>22°C Vehicle</b>	2409	100	0.067	6153	2.6	0.44
<b>22°C CL316243</b>	2927	145	1.79	8362	44	15
<b>30°C Vehicle</b>	526	0.45	0.071	1727	1.4	0.25
<b>30°C CL316243</b>	2491	0.92	0.26	5482	3.2	3.4

For global comparisons of Ucp1 mRNA levels, the Ucp1 mRNA:18S RNA ratios are presented using a common reference scale (chow, 22°C, vehicle, iWAT arbitrarily set to 100). Data are means, recalculated from Figures 2C-E and 5C-E. HFD, high fat diet; BAT, brown adipose tissue; iWAT, inguinal white adipose tissue; eWAT, epididymal white adipose tissue.

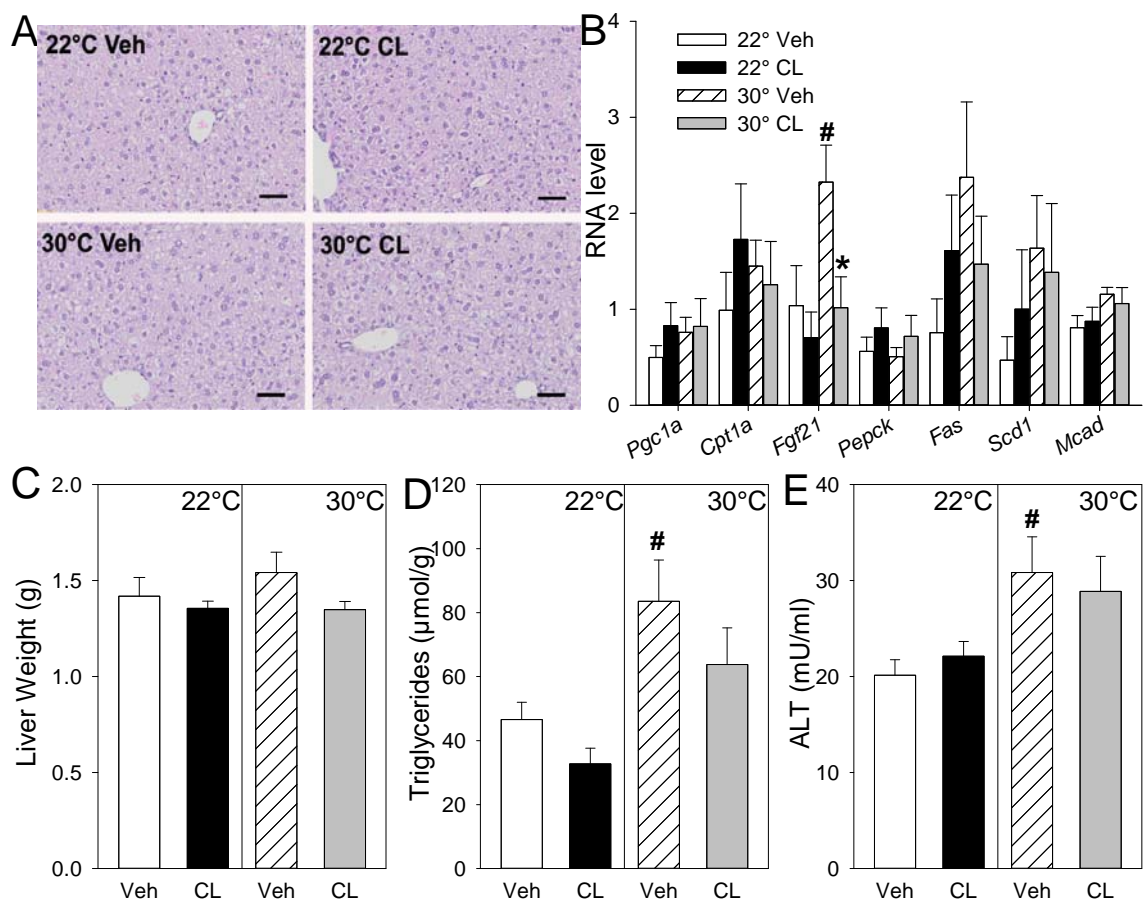
Log-transformed Ucp1 mRNA levels were analyzed with a standard least squares model (JMP version 11.0.0, SAS Institute Inc, Cary, NC). When tissue was included in a global model, it dominated the model. Thus, each tissue was analyzed separately, with temperature, drug, and diet as independent factors (61-63 observations/tissue). The adjusted  $r^2$  are 0.69 (BAT), 0.62 (iWAT), and 0.76 (eWAT) and the parameter estimates are:

	<b>BAT</b>			<b>iWAT</b>			<b>eWAT</b>		
	Estimate	t Ratio	Prob> t	Estimate	t Ratio	Prob> t	Estimate	t Ratio	Prob> t
Intercept	3.420	121	<0.0001	0.549	6.2	<0.0001	-0.356	-7.0	<0.0001
Diet	-0.206	-7.3	<0.0001	0.093	1.0	0.30	-0.379	-7.5	<0.0001
Drug	0.170	6.0	<0.0001	0.392	4.4	<0.0001	0.521	10.3	<0.0001
Temperature	0.197	7.0	<0.0001	0.797	8.9	<0.0001	0.221	4.4	<0.0001
Standard error	0.028			0.089			0.051		

When all pair-wise interactions were included, the adjusted  $r^2$  was 0.76 (BAT), 0.76 (iWAT), and 0.81 (eWAT) and the significant interactions (all  $P < 0.0001$ ) were: BAT, temperature x drug; iWAT, temperature x diet; and eWAT, temperature x drug.



**Figure S1.** Effect of CL316243 on liver in chow fed mice. **A**, histology; **B**, mRNA levels; **C**, liver weight; **D**, liver triglycerides; **E**, serum alanine aminotransferase (ALT). Scale bar, 50  $\mu$ m. Tissues and serum were collected at euthanasia after 4 weeks of CL316243 or vehicle treatment. mRNA levels are normalized to 22°C vehicle. Data are mean  $\pm$  S.E.; n=8/group. #, p<0.05 for vehicle-vehicle comparison at different environmental temperatures.



**Figure S2.** Effect of CL316243 on liver in HFD fed mice. **A**, histology; **B**, mRNA levels; **C**, liver weight; **D**, liver triglycerides; **E**, serum alanine aminotransferase (ALT). Scale bar, 50  $\mu\text{m}$ . Tissues and serum were collected at euthanasia after 4 weeks of CL316243 or vehicle treatment. mRNA levels are normalized to 22°C vehicle from chow fed experiment. Data are mean  $\pm$  S.E.;  $n=8/\text{group}$ . #,  $p<0.05$  for vehicle-vehicle comparison at different environmental temperatures; \*,  $p<0.05$  for vehicle-CL316243 comparison, within temperature.