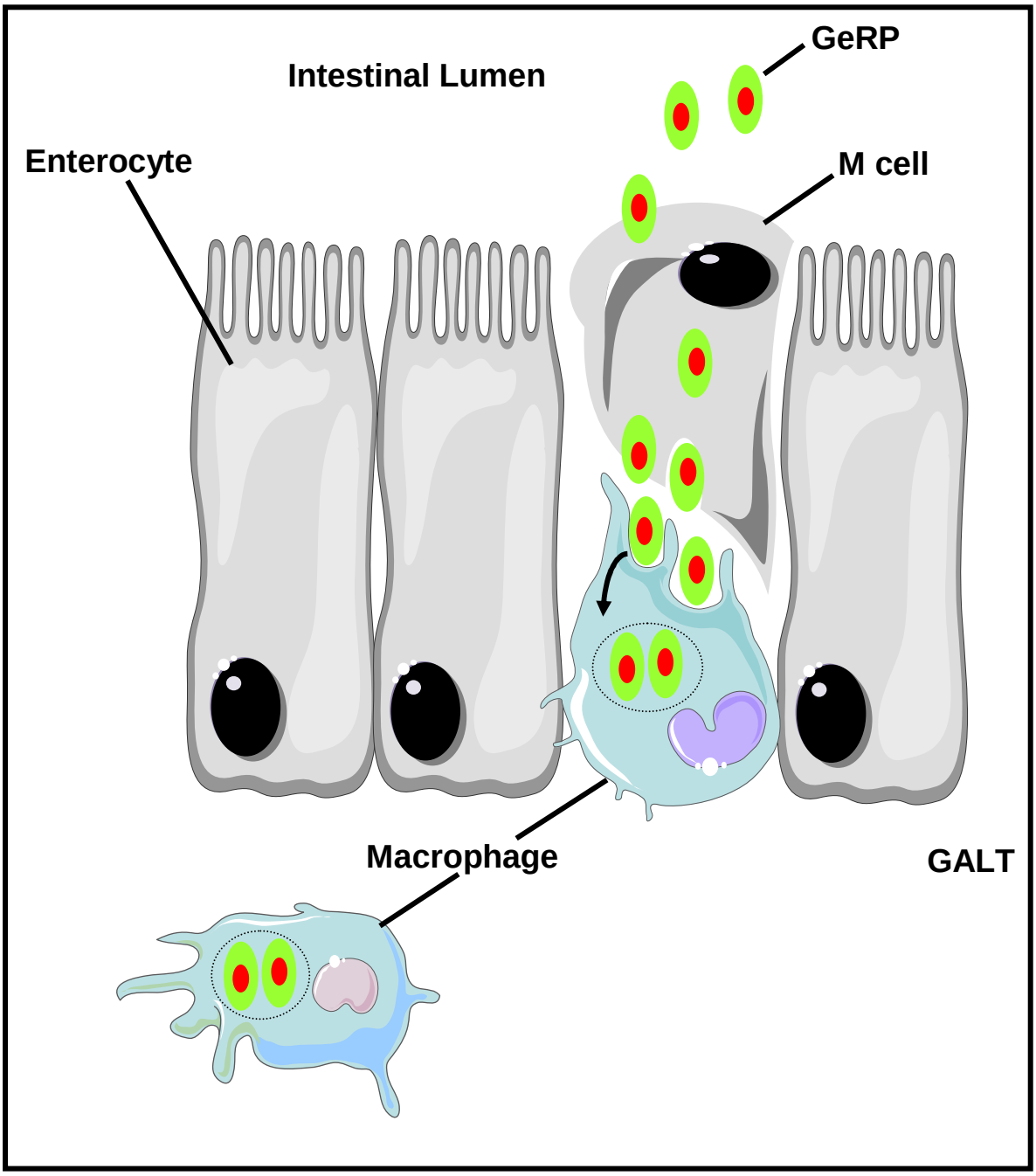
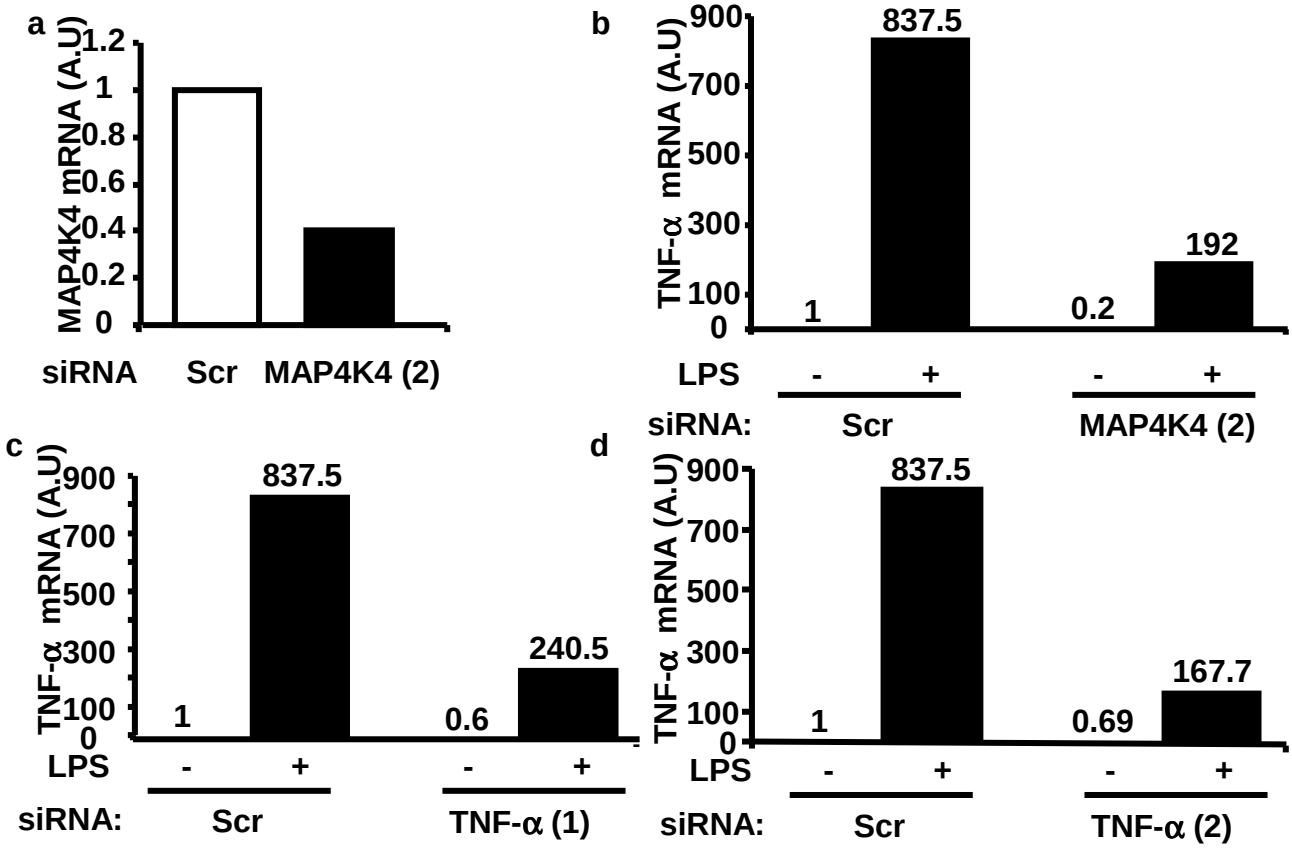
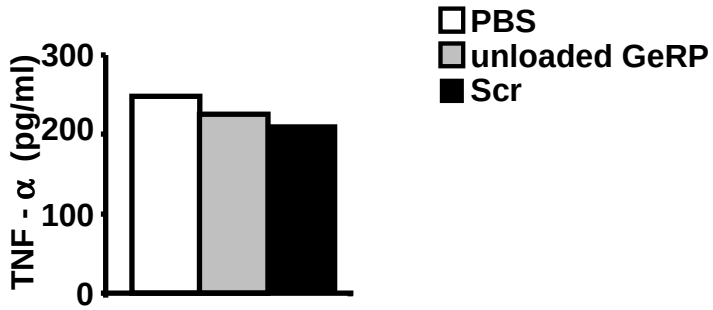


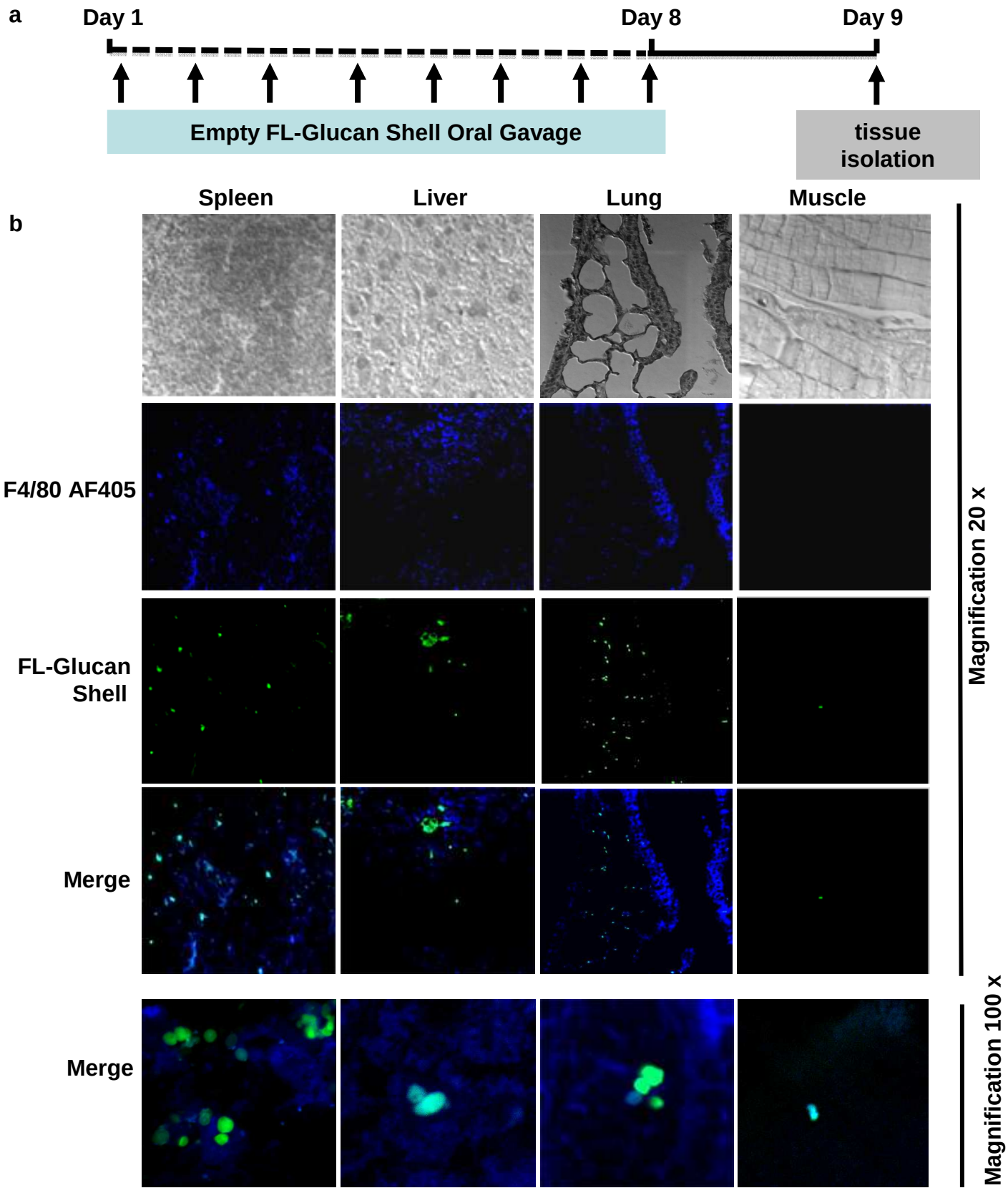
Supplementary Figure 1. **Model for GeRP uptake by macrophages in the gut associated lymphatic tissue (GALT).** GeRPs in the intestinal lumen enter M cells and gain access to GALT macrophages. Gastrointestinal macrophage phagocyte GeRP and transport them to various tissues such as spleen, liver and lung.



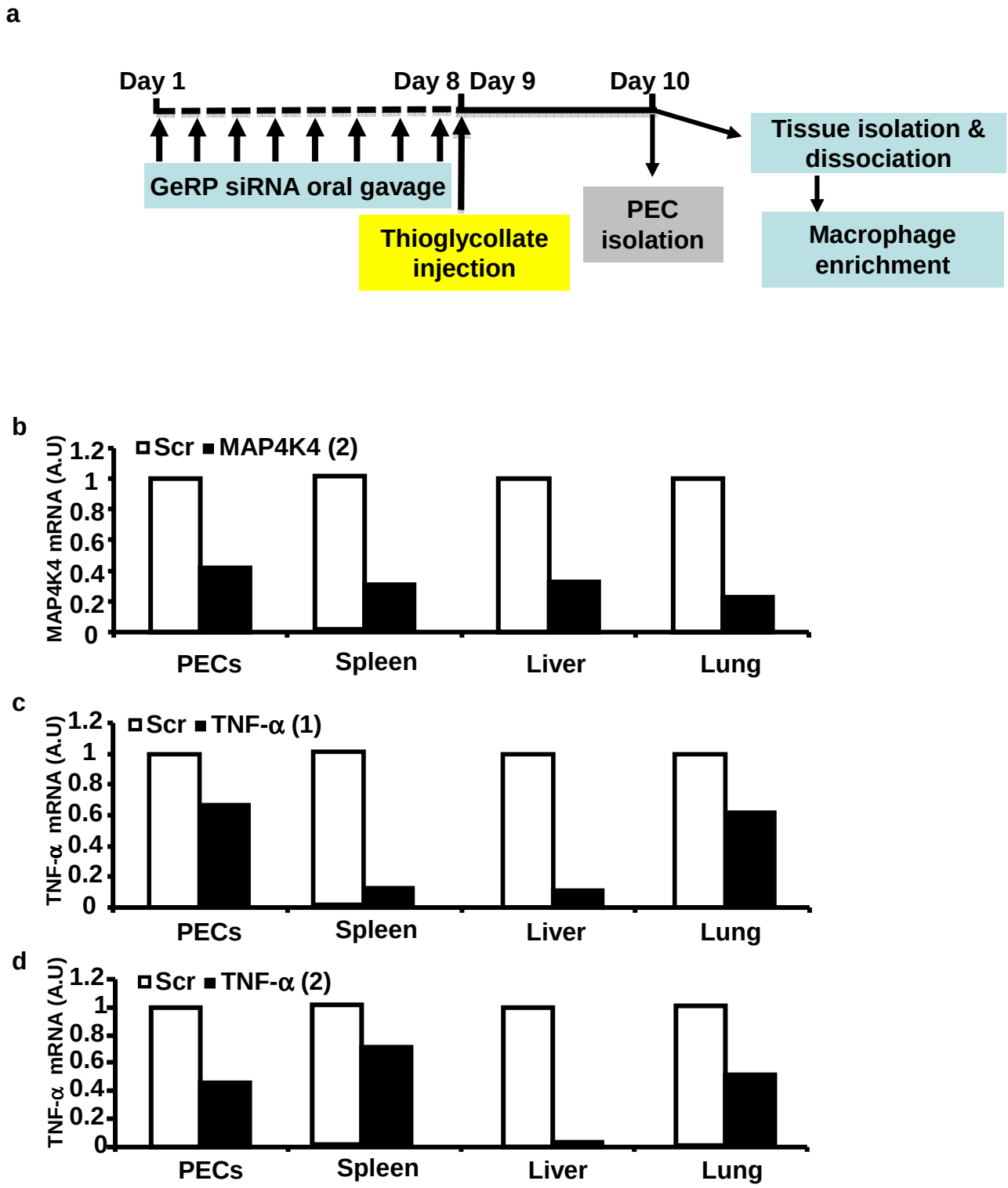
Supplementary Figure 2. **A second siRNA targeting MAP4K4 or two distinct TNF-α siRNA effectively silence MAP4K4 and TNF-α mRNA expression, respectively. (a)** 10^6 PECs were treated with 10^7 GeRPs loaded with 20 ug/kg of Scr or a second MAP4K4 siRNA: MAP4K4 (2). Total RNA was harvested 48 hours after treatment and analyzed by real time PCR for the expression of MAP4K4 mRNA. **(b)** LPS-induced TNF-α expression in PECs treated with Scr- or MAP4K4 (2) siRNA-GeRPs, **(c)** and **(d)** LPS-induced TNF-α expression in PECs treated with GeRPs loaded with 20 ug/kg of Scr, TNF-α (1) or TNF-α (2) siRNA.



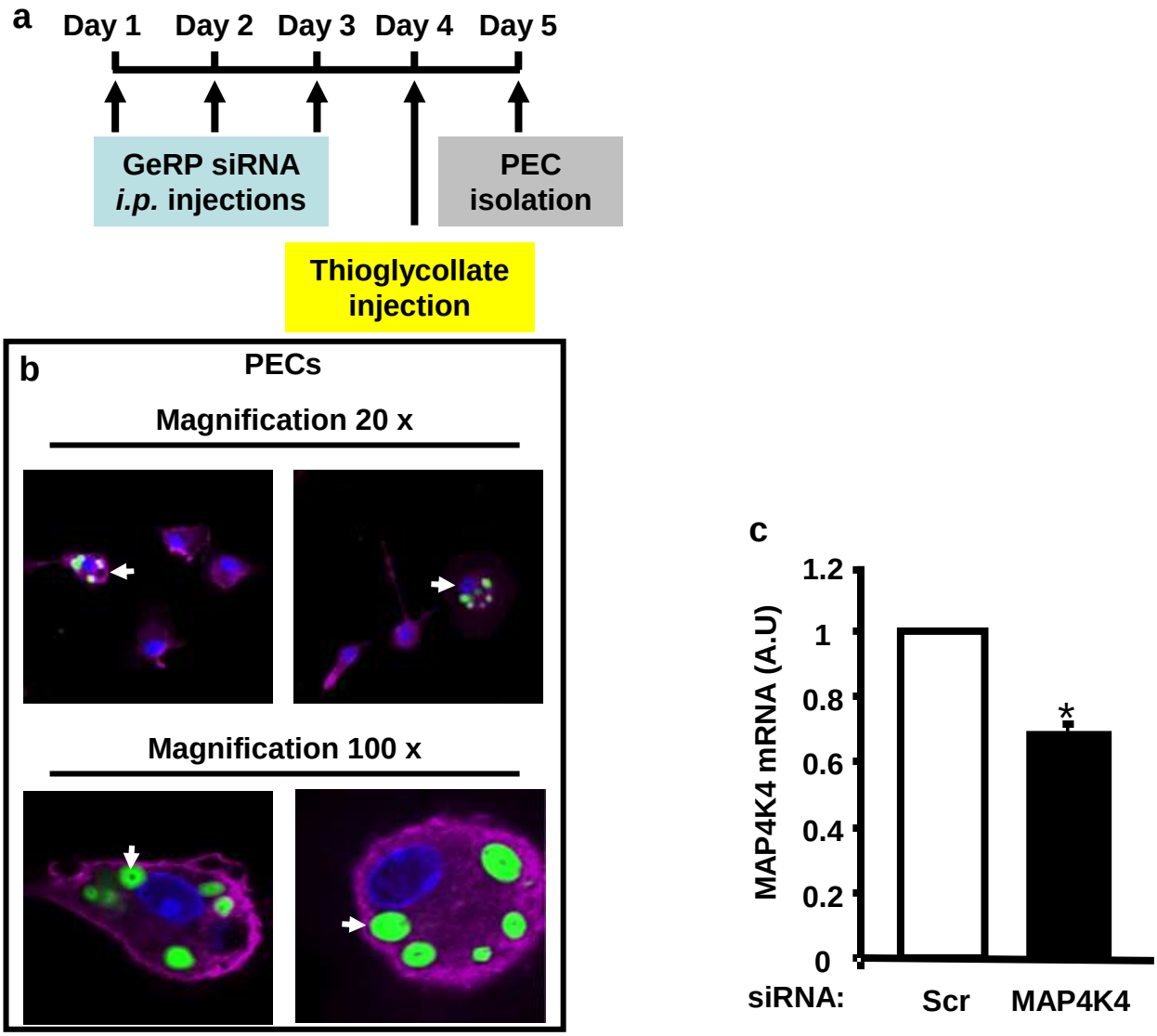
Supplementary Figure 3. GeRPs loaded with scramble siRNA or unloaded GeRPs have no effect on LPS-induced TNF-α secretion. (a) 10^6 PECs were treated with PBS, 10^7 unloaded GeRPs or GeRPs loaded with 20ug/kg of Scr. TNF-α levels in PEC media was measured by ELISA.



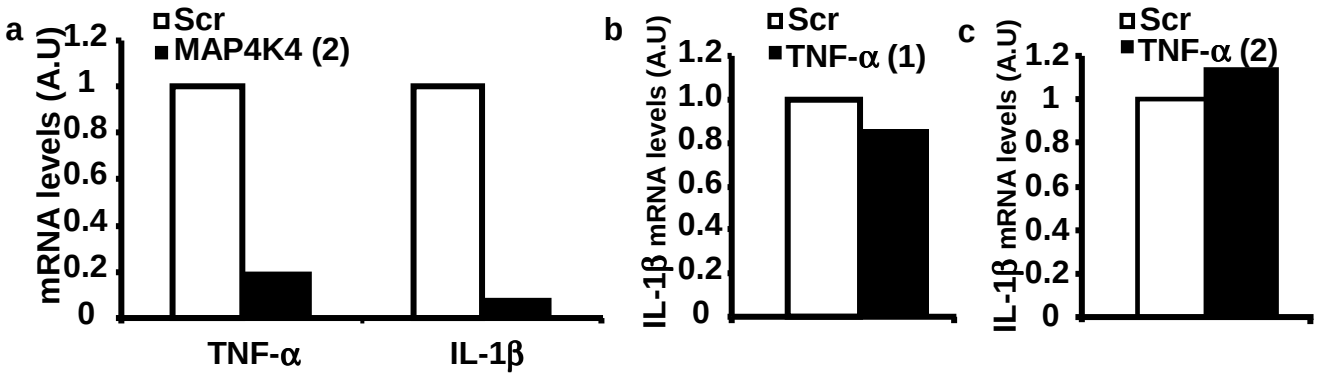
Supplementary Figure 4. Orally administered FL-glucan shells are taken up by migratory gut macrophages and traffic into spleen, liver and lung. (a) Timeline of oral administration of FL-glucan shells and tissue collection. Animals were on a high fat diet for 12 weeks before treatment. **(b)** Staining with F4/80-AF405 confirmed that spleen, liver and lung macrophages contained FL-glucan shells (green). Upper panels, magnification: 20x and lower panel, magnification: 100x.



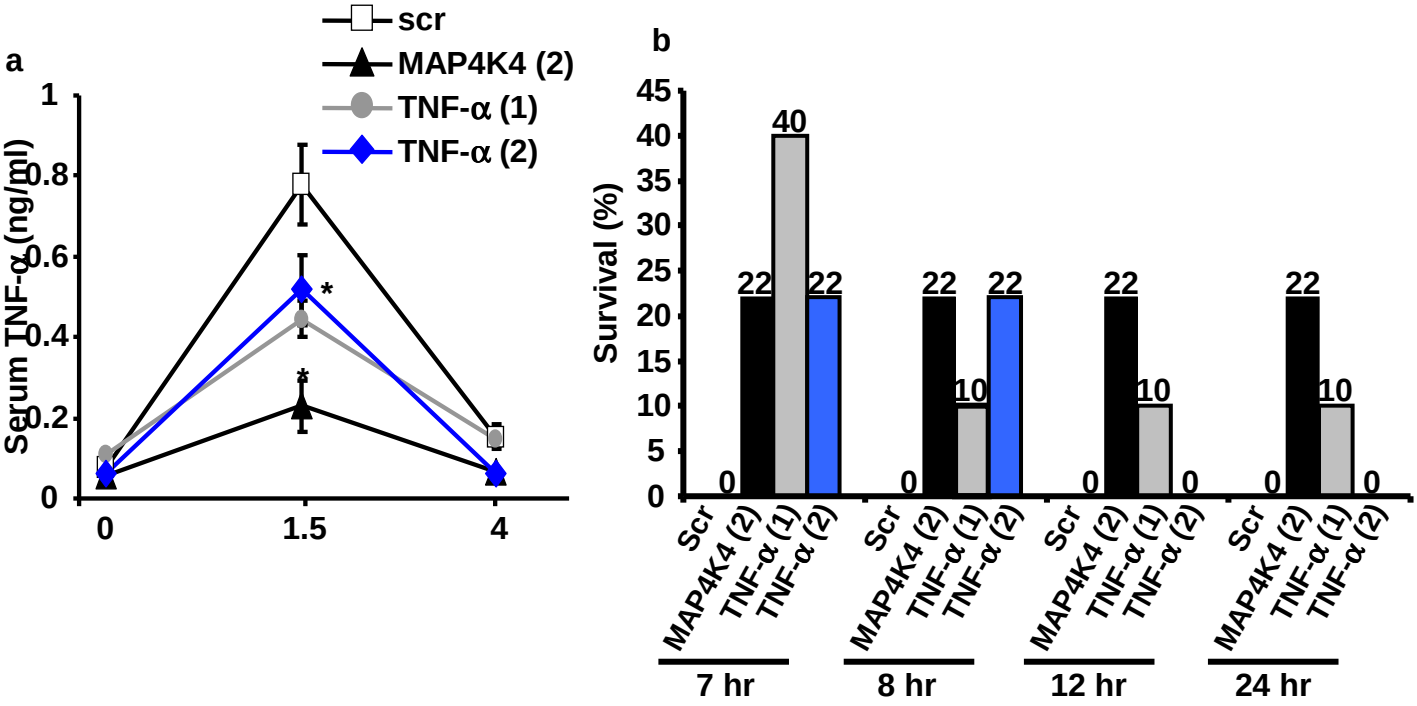
Supplementary Figure 5. Orally administered GeRPs containing a second MAP4K4 siRNA or TNF-α siRNA silence MAP4K4 and/or TNF-α expression in PECs, and spleen, liver and lung macrophages. Analysis of MAP4K4 or TNF-α expression PECs and adherent cells isolated from spleen, liver and lung from mice gavaged with GeRPs loaded with 20 ug/kg of Scr, **(a)** a second siRNA targeting MAP4K4: MAP4K4 (2), or two siRNAs against TNF-α, **(b)** TNF-α (1) or **(c)** TNF-α (2).



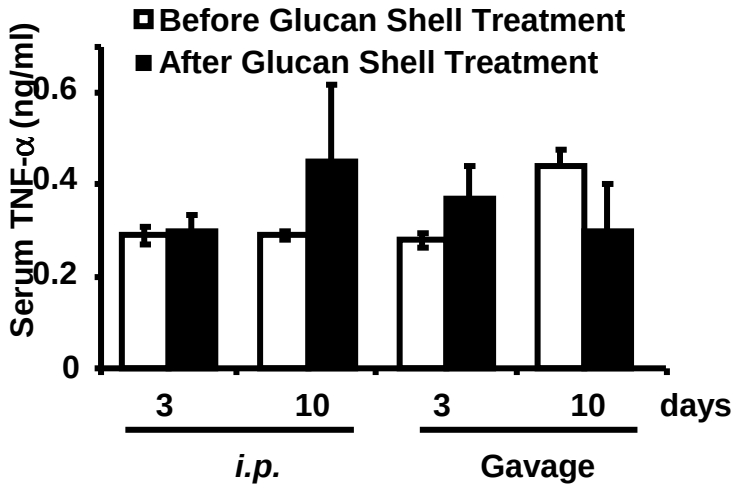
Supplementary Figure 6. *i.p.* administration of GeRPs containing MAP4K4 siRNA reduce MAP4K4 mRNA expression in macrophages in vivo. (a) Timeline of *i.p.* treatment with siRNA-GeRPs and PEC isolation. **(b)** Confocal microscopy of PECs. Staining with F4/80-AF633 (Magenta) confirmed that PECs contained GeRPs (green). Nuclei were stained with Dapi (blue). Arrows point to representative GeRPs. Upper panels, magnification: 20x and lower panel, magnification: 100x. **(c)** MAP4K4 mRNA expression. Results are expressed in arbitrary units and are the mean $\pm$ SEM of four independent experiments. Significance was determined using Student's t-test * $p < 0.001$.



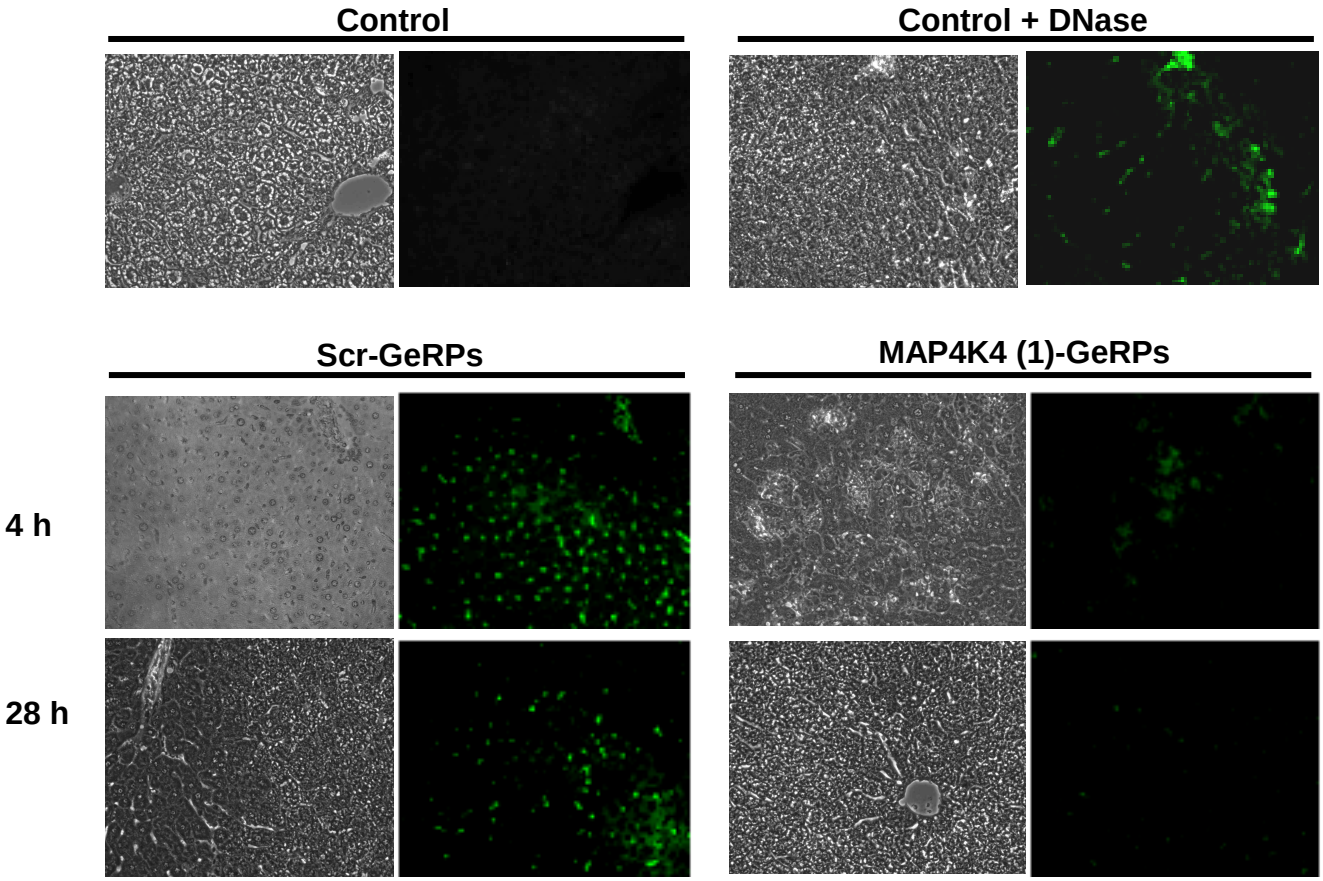
Supplementary Figure 7. MAP4K4, but not TNF-α silencing inhibits IL-1β expression. Expression of TNF-α and/or IL-1β in PECs isolated from mice orally treated with GeRPs containing 20 ug/kg of scr, MAP4K4 (2), TNF-a (1) or TNF-a (2) siRNA .



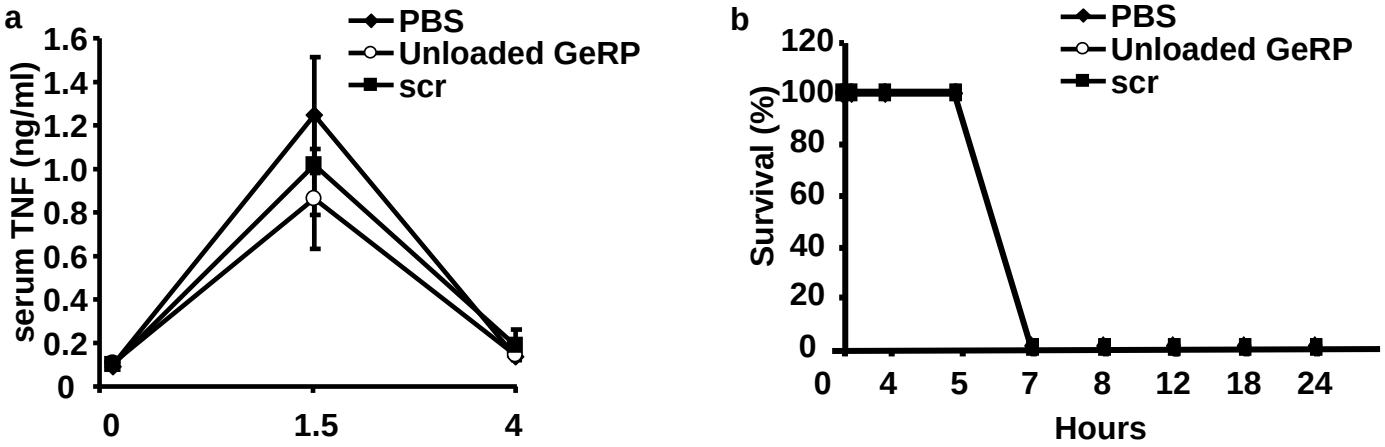
Supplementary Figure 8. A second siRNA targeting MAP4K4 inhibits LPS-induced TNF-a production and lethality *in vivo*. Mice were gavaged with siRNA-GeRPs. Four hours after the final gavage, mice were *i.p.* injected with D-GalN, followed by an *i.p.* injection of LPS. **(a)** Serum TNF-a levels in siRNA treated mice 1.5 and 4 hours after LPS/D-GalN injection. Results are the mean ± SEM (n=5). Statistical significance was determined by ANOVA and Tukey post test; *p <0.05. (**b**) Percent survival of mice orally treated with siRNA-GeRPs followed by LPS/D-GalN injections.



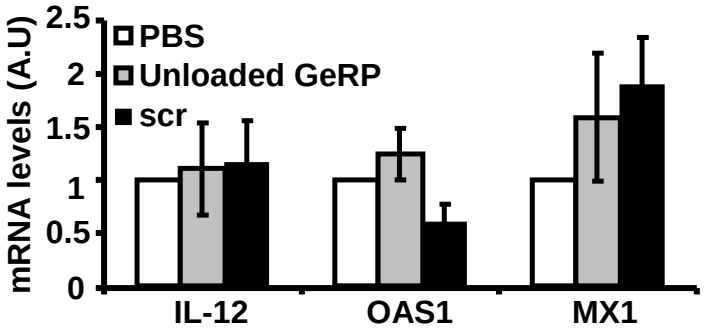
Supplementary Figure 9. Administration of glucan shells by *i.p*. injection or oral gavage fails to change TNF-alpha levels in serum. Serum TNF-α levels in the absence of LPS before and after the administration of empty glucan shells by *i.p* injection or by oral gavage.



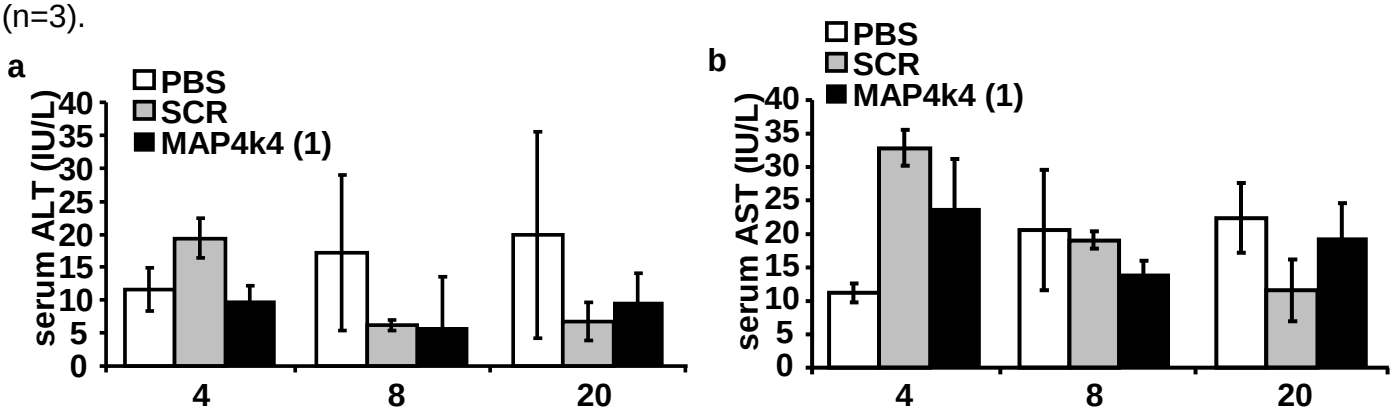
Supplementary Figure 10. TUNEL assay shows MAP4K4 containing GeRPs protects against LPS/D-GalN liver toxicity. Silencing MAP4K4 inhibits LPS/D-GalN -induced apoptosis in liver 4 and 28 hours after LPS/D-GalN injection. Livers from untreated mice were treated with or without DNase and used as positive and negative controls, respectively.



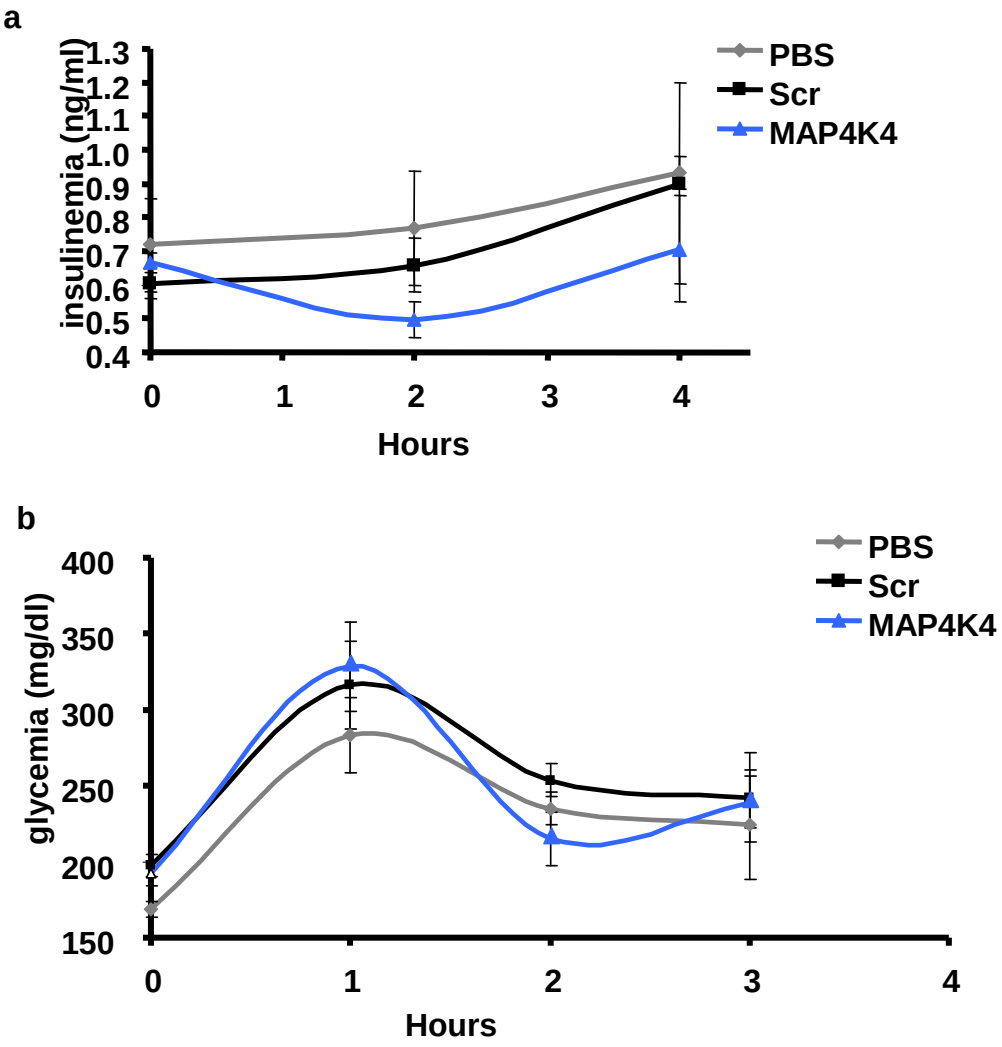
Supplementary Figure 11. Unloaded GeRPs or GeRPs loaded with scramble siRNA have no effect on LPS-induced TNF-a production and lethality *in vivo.* Mice were gavaged with unloaded GeRPs or GeRPs loaded with 20 ug/kg of Scr siRNA. Four hours after the final gavage, mice were *i.p.* injected with D-GalN, followed by an *i.p.* injection of LPS. **(a)** Serum TNF-a levels were measured 1.5 and 4 hours after LPS/D-GalN injection. Results are the mean ± SEM (n=5). Statistical significance was determined by ANOVA and Tukey post test. **(b)** Percent survival of mice orally treated with siRNA-GeRPs, and then injected with LPS/D-GalN. Survival was assessed every hour for 24 hours.



Supplementary Figure 12. siRNA-GeRPs failed to elicit an interferon response *in vitro*. 10^6 PECs were treated with PBS, 10^7 unloaded GeRPs or GeRPs loaded with Scr siRNA. Total RNA was harvested 48 hours after treatment and analyzed by real time PCR for the expression of INFβ target genes, OAS1 and MX1 or INFγ target genes, IL-12. Results are the mean ± SEM (n=3).



Supplementary Figure 13. siRNA-GeRP oral treatment fails to alter serum liver enzyme levels *in vivo*. Mice were gavaged with PBS or GeRPs containing 20 ug/kg of Scr or MAP4K4 (1) siRNA. **(a)** Alanine aminotransferase (ALT) and (**b**) aspartate aminotransferase (AST) were measured in serum 4, 8 and 20 days after the last gavage (n=3).



Supplementary Figure 14. MAP4K4 silencing fails to affect LPS regulation of blood glucose and insulin levels. Mice were gavaged with PBS or GeRPs loaded with 20 ug/kg of Scr or MAP4K4 (1) siRNA. Four hours after the final gavage, mice were *i.p.* injected with D-GalN, followed by an *i.p.* injection of LPS. **(a)** Serum insulin levels 2 and 4 hours after LPS/D-GalN injection. **(b)** Serum glucose levels 1, 2 and 3 hours after LPS/D-GalN injection. Results are the mean ± SEM (n=5). Statistical significance was determined by ANOVA and Tukey post test.

	Accession numbers	siRNA sequence	Percentage *in vitro* knockdown	Percentage *in vivo* knockdown
Scramble	–	5'-CAGUCGCGUUUGCGACUGG-3'	0	0
Map4K4 (1)	NM_008696	5'-GACCAACUCUGGCUUGUUA-3'	72	70
Map4K4 (2)		5'-CAGAAGUGGCCAAGGGAAA-3'	60	60
TNF-α (1)	NM_013693	5'-GACAACCAACUAGUGGUGC-3'	40	33
TNF-α (2)		5'-GCAUGGAUCUCAAAGACAA-3'	31	54

Supplementary Table 1. *in vitro* and in vivo knockdown with various siRNA-GeRPs

Hours after *LPS/D-Galactosamine Injection*	*Number of Mice Surviving at Indicated Time Point*		
	PBS	Scr	MAP4K4
0	11/11	22/22	22/22
6	4/11	14/22	18/22
7	1/11	3/22	15/22
8	1/11	2/22	11/22
10	1/11	2/22	9/22
24	1/11	2/22	8/22

Supplementary Table 2. Survival post LPS-challenge of mice treated with PBS, Scr or MAP4K4 (1) siRNA-GeRPs.

	Chi-Square	Df	Sig.
Log Rank	8.334	1	0.004
Breslow	8.799	1	0.003
Tarone-Ware	8.99	1	0.003

Supplementary Table 3. Statistical testing of the equality of survival probabilities between Scr and MAP4K4 (1) siRNA-GeRP treatments in the LPS/D-galactosamine challenge.

Primer	Sequence
36B4 F	TCCAGGCTTTGGGCATCA3
36B4 R	CTTTATCAGCTGCACATCACTCAGA
MAP4K4 F	CATCTCCAGGGAAATCCTCAGG
MAP4K4 R	TTCTGTAGTCGTAAGTGGCGTCTG
TNF-a F	CCCTCACACTCAGATCATCTTCT
TNF- a R	GCTACGACGTGGGCTACAG
IL-1b F	GCAACTGTTCCTGAACTCAACT
IL-1 b R	ATCTTTTGGGGTCCGTCAACT
IL-10 F	CTGGACAACATACTGCTAACCG
IL-10 R	GGGCATCACTTCTACCAGGTAA
CCR2-F	ATCCACGGCATACTATCAAGATC
CCR2-R	CAAGGGTCACCATCATGGTAG
OAS1-F	ATTACCTCCTTCCCGACACC
OAS1-R	CAAACTCCACCTCCTGATGC
MX1-F	GATCCGACTTCACTTCCAGATGG
MX1-R	CATCTCAGTGGTAGTCAACCC
IL-12p40	AGACATGGAGTCATAGGCTCTG
IL-12p40	CCATTTTCCTTCTTGTGGAGCA

Supplementary Table 4 Primer sequences