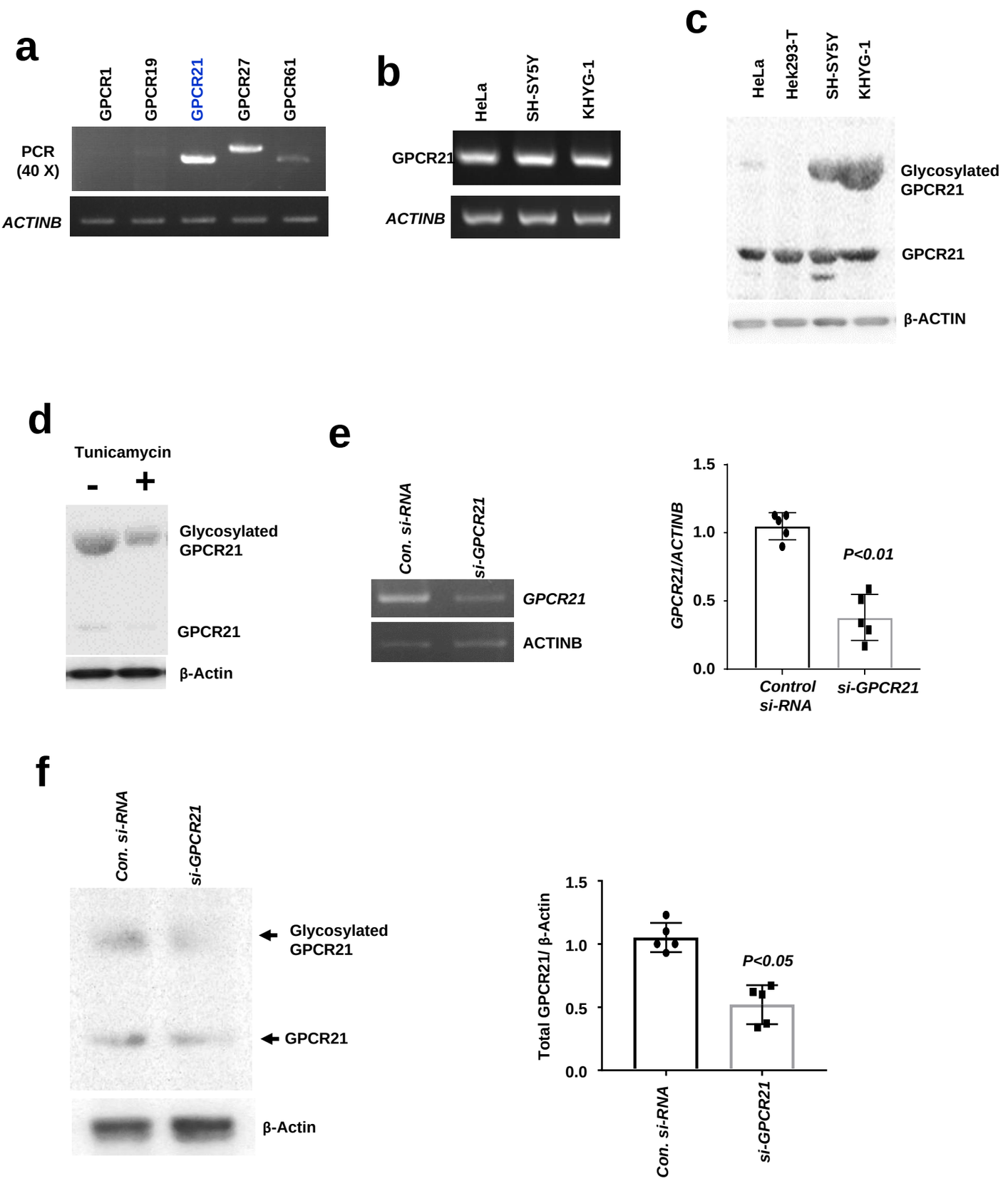
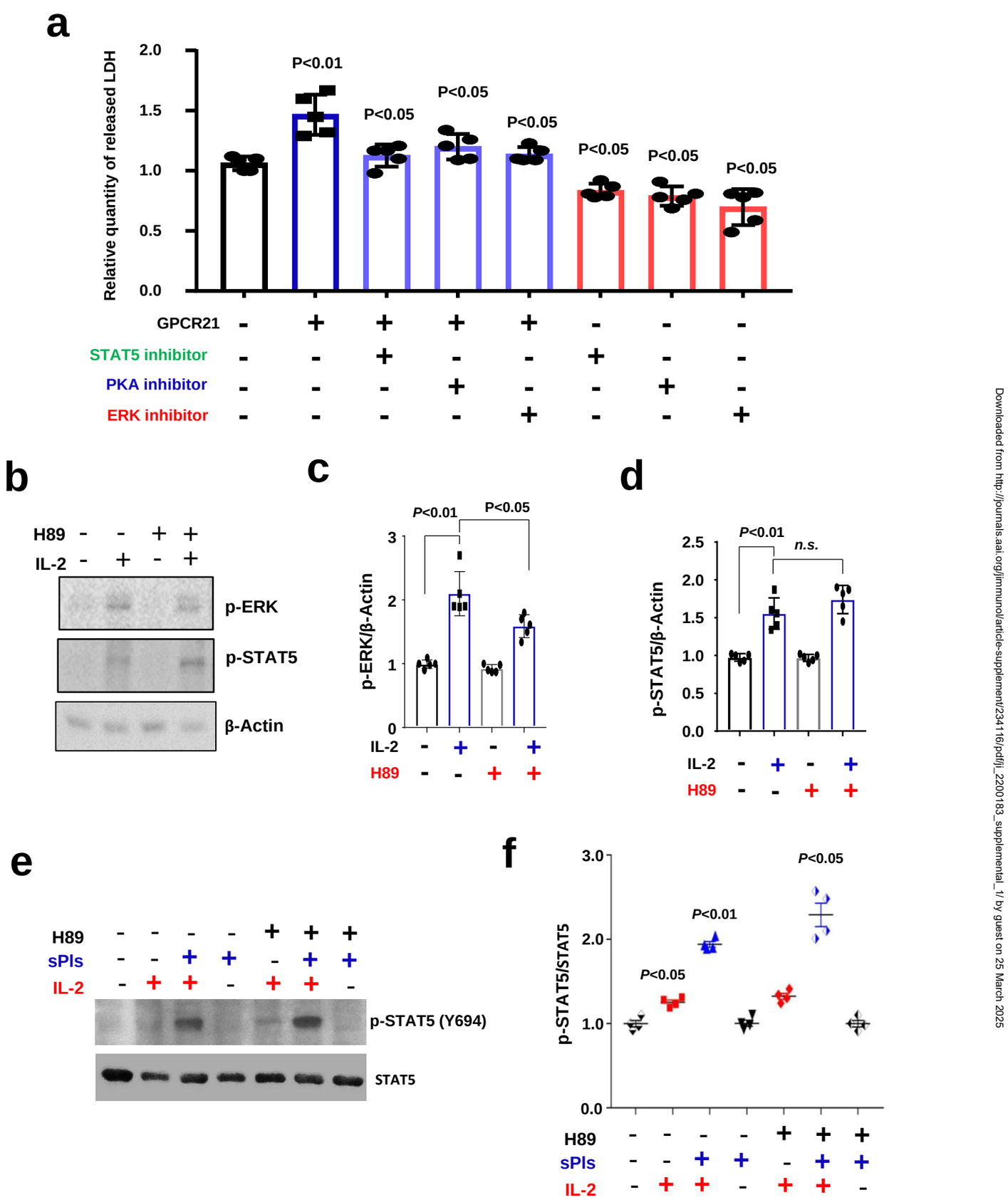
Supplementary Figure 1



Suppl. Fig. 1. GPCR expression in human NK cells

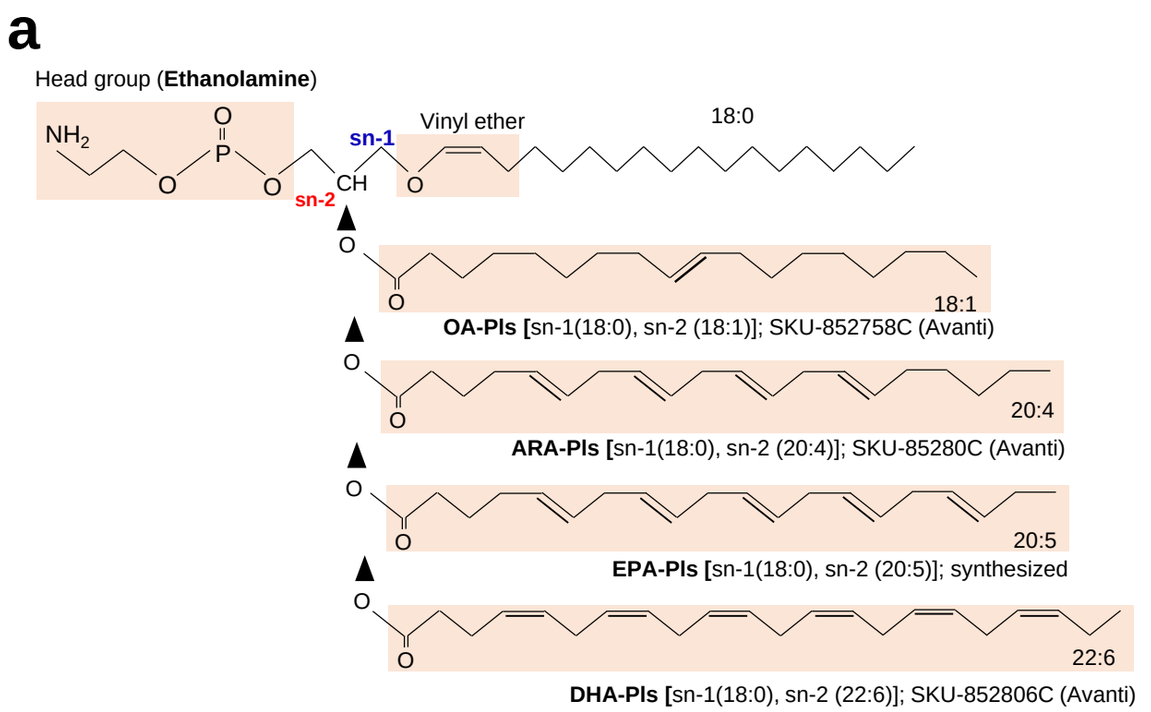
a PCR analysis showing endogenous mRNA expression of GPR1, GPR19, GPCR21, GPR27 and GPR61 in KHYG-1 cells (data represent three independent experiments, n = 3). **b** PCR analysis showing endogenous GPCR21 expression in the indicated cells. ACTINB was used as internal control. **c** Immunoblotting assays of endogenous GPCR21 expression in the indicated cells (n = 3). **d** Immunoblotting of GPCR21 in KHYG-1 cells after 12-hour tunicamycin (5 μM) treatments (n = 3). **e, f** PCR and immunoblotting assays of KHYG-1 cells transfected with control si-RNA (SIC001, universal negative control, Sigma) and siRNA against GPCR21 (mission siRNA, Sigma) in a dose of 10 pmol/10^4 cells. **e** Gel electrophoresis (left) and quantification of PCR bands of GPCR21 (right). **f** Immunoblotting of GPCR21 (left) and quantification of GPCR21 (right). The quantification values represented mean SEM and the P values were calculated by student's t-test (n = 4, $P < 0.01$ and $P < 0.05$) (**e**, **f**).

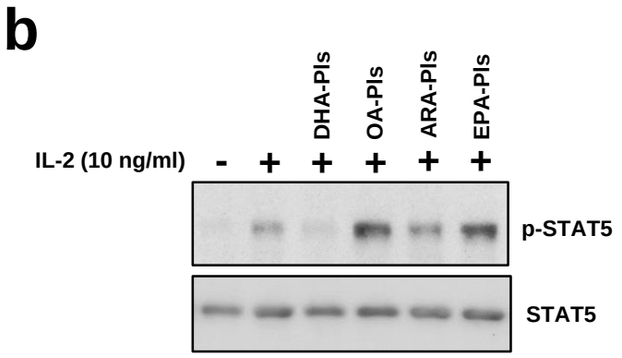
Supplementary Figure 2

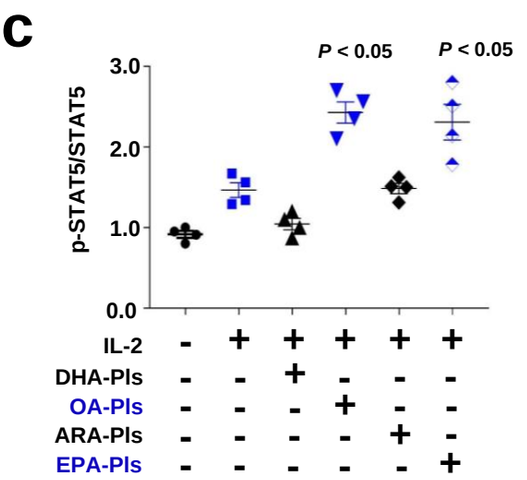


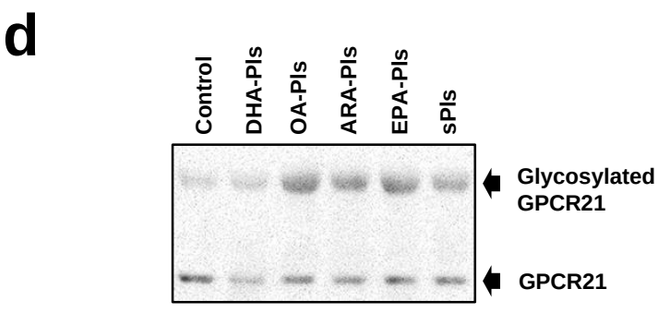
Suppl. Fig. 2. PKA, ERK and STAT5 inhibitors attenuate GPCR21-mediated cytotoxic activity
a Quantification of LDH released by K562 cancer cells after co-culture with GPCR21-overexpressed KHYG-1 cells (Data represent mean ± SEM of 5 samples in each group n = 5; E:T = 10:1). KHYG-1 cells were cultured in the presence of IL-2 (10 ng/ml) and pretreated with or without the inhibitors of STAT5 (285986-31-4,10 μM), PKA (H89, 5 μM) and ERK (U0126, 5 μM) for 12 hours. **b**, **c**, **d** Immunoblotting assays of KHYG-1 pretreated with or without H89 (5 μM) for 12 hours followed by IL-2 treatments (10 ng/ml) for 20 minutes (n = 3). **b** Immunoblotting of the indicated proteins (the data represent three independent experiments). **c** Quantification of pERK. d Quantification of pSTAT (mean ± SEM). **e**, **f** Immunoblotting assays of KHYG-1 cells pre-treated with or without PKA inhibitor (H89 5 μM) for 12 hours followed by treatments with IL-2 (10 ng/ml) and sPls (5 μg/ml) for 20 minutes (n = 4). **e** Representative immunoblotting image of the indicated proteins. **f** Quantification of pSTAT (mean ± SEM). P values were calculated by ANOVA followed by the Bonferroni's post hoc test (**a**, **c**, **d**, **f**).

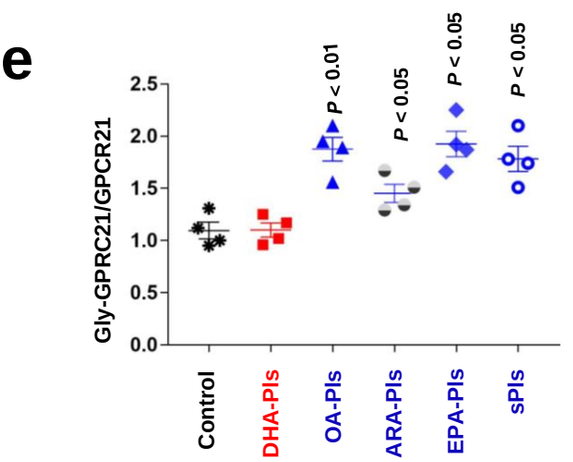
Supplementary Figure 3





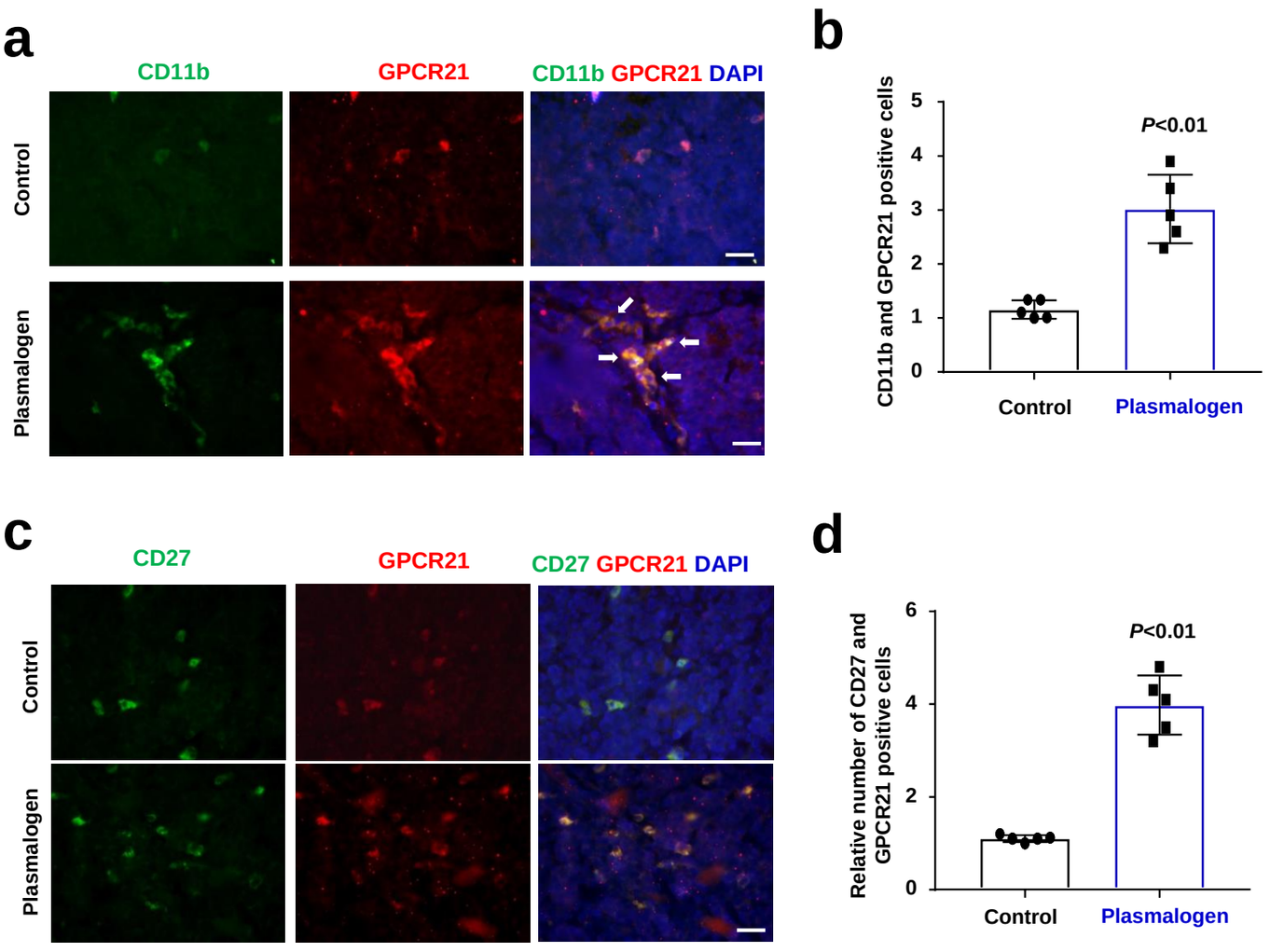






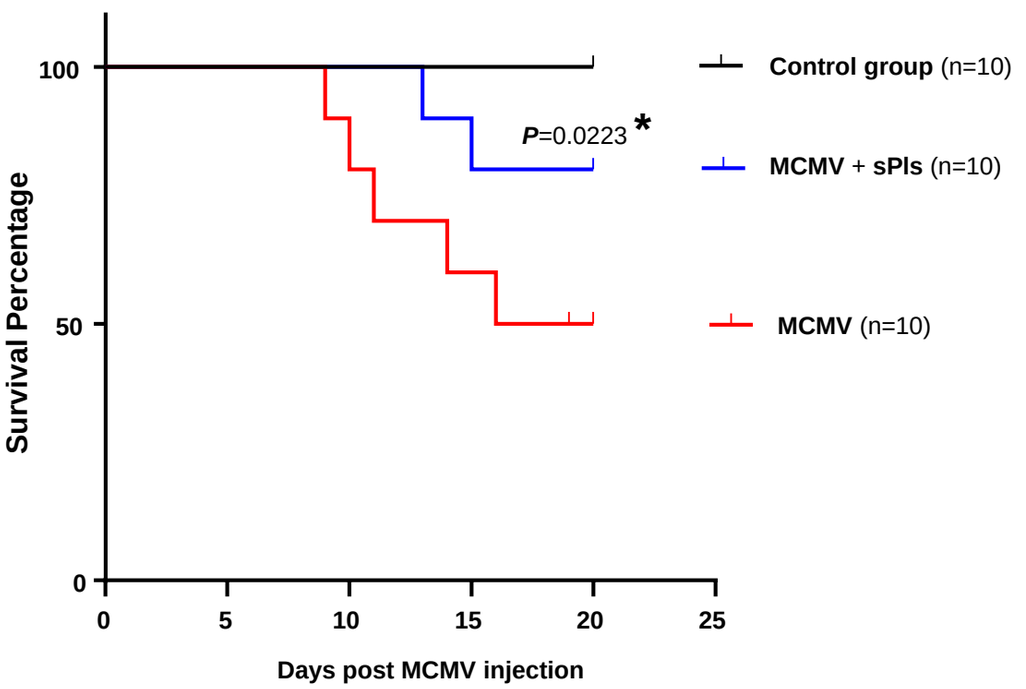
Suppl. Fig. 3. PlsEtn enhances phosphorylation of STAT5 in NK cells
a Chemical structure of PlsEtn containing different kinds of long-chain fatty acids, OA, ARA, EPA, and DHA, at the sn-2 position. EPA-PlsEtn were synthesized and purified by our collaborator (data can be provided upon request). **b**, **c** Immunoblotting assays of KHYG-1 cells pretreated with indicated PlsEtn (5 μg/ml each) for 24 hours followed by 20-minute IL-2 treatments (10 ng/ml) (n = 4). **b** Representative immunoblotting image of indicated proteins. c Quantification of p-STAT. Protein levels are normalized to total STAT5. **d**, **e** Immunoblotting assay of KHYG-1 cells cultured in medium supplemented with IL-2 (2 ng/ml) and 5% FBS followed by 20-minute treatments with indicated PlsEtn (5 μg/ml each) (n = 4). **d** Representative immunoblotting image of GPCR21 in 50μg protein extracts of each sample. **e** Quantification of glycosylated GPCR21. Protein levels are normalized to total GPCR21. Values represent the mean ± SEM, and the P values were calculated by ANOVA followed by the Bonferroni's post hoc test (**c**, **e**).

Supplementary Figure 4



Suppl. Fig. 4. Pls drinking enhances GPCR21 expression in murine NK cells
Immunohistochemistry (IHC) staining analyses of frozen sections of xenograft tumor tissues taken from five mice in each group (n = 5). a Representative fluorescence microscopy imaging of CD11b (green), GPCR21 (red), and DAPI (blue). White allows point to CD11b-positive NK cells expressing GPCR21 as well (merged yellow color) in the Pls group. The scale bar indicates 50 μm. b A relative change in the number of CD11b- and GPCR21-positive cells. c Representative fluorescence microscopy imaging of CD27 (green), GPCR21 (red), and DAPI (blue). Yellow color indicates CD27-positive NK cells expressing GPCR21 as well. d A relative change in the number of CD27- and GPCR21-positive cells. The P values were calculated by student's t-text (P<0.01) (b, d).

Supplementary Figure 5



Suppl. Fig. 5. Pls drinking enhances survival rate in the virus infected mice
Kaplan-Meier survival curves show the mortality rate among the mice groups (ten mice in each group, n=10). The significant value (***P*** = 0.0234) among the groups were calculated by log-rank (Mantel-Cox) test using GraphPad Prism-7 software.