Supplemental Figures

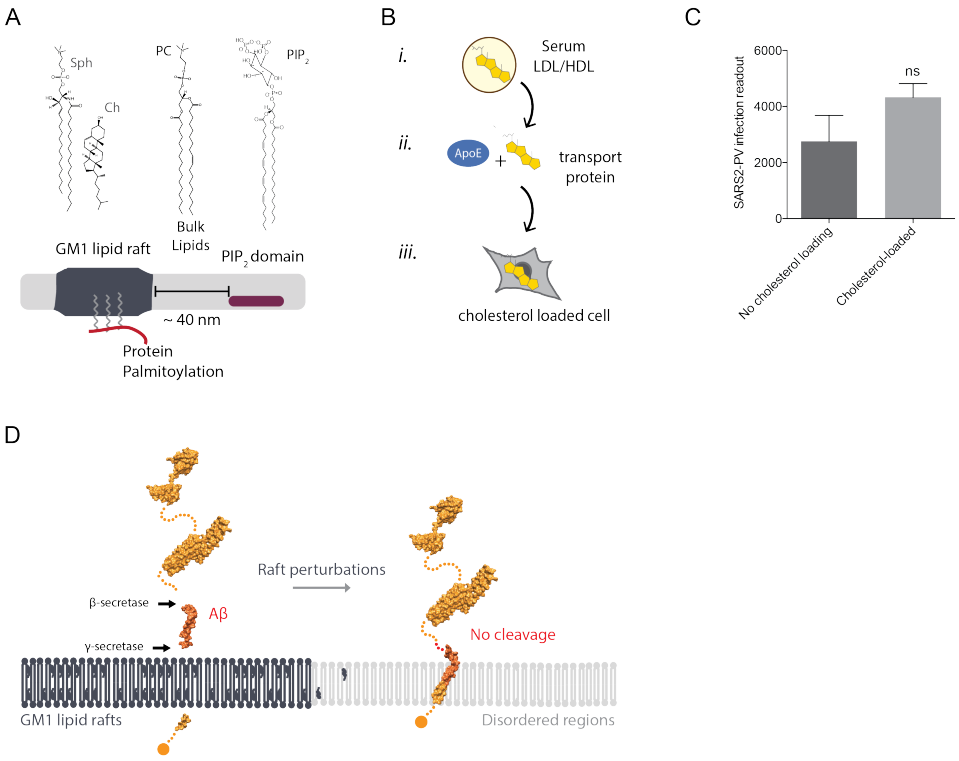

Fig. S1. Membrane heterogeneity. (A) GM1 rafts are clusters of saturated known as liquid ordered (L_o) and commonly reside separate from liquid disordered (L_d) phases[62]. The ordered phase (L_o) is generally enriched in sphingomyelin and cholesterol whereas the disordered (L_d) phase consists of unsaturated lipids and includes polyunsaturated lipids like PA and PIP_2[64]. **(B)** Cartoon diagram showing the experimental setup for loading cultured cells with cholesterol. ***i.***, Cholesterol (yellow shading) loaded into lipoprotein (e.g., low- and high-density lipoprotein (LDL and HDL respectively)) from blood serum. ***ii.***, Cholesterol free human apolipoprotein E (apoE, brown shading), a cholesterol transport protein, is exposed to cholesterol from blood serum and ***iii,*** ApoE transports cholesterol into of cells (grey shading). **(C)** SARS2-PV entry in ACE2 overexpressing HEK293T cells without and with cholesterol loading indicated by raw luciferase activity readout. Data are expressed as mean ± s.e.m., unpaired t-test, n=4. **(D)** Model of HCQ and anesthetics translocating APP from GM1 rafts to disordered regions through raft perturbation to reduce the synthesis of Aβ.

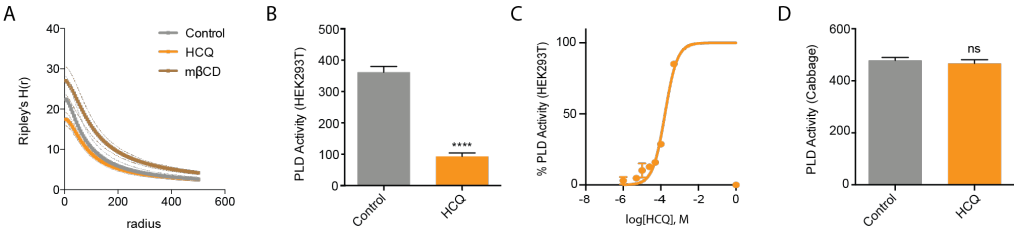

Fig. S2. HCQ displacement of PLD2 from lipid rafts. (A) Ripley's H -Function (H(r)) showing raft separation. **(B)** HCQ (50μM) decreased PLD activity in PLD assay. Data are expressed as mean ± s.e.m., ****P ≤ 0.0001, unpaired t test, n=6. **(C)** A dose response of HCQ's inhibition to PLD activity in PLD assay, n=3. **(D)** Effect of HCQ(50μM) on PLD activity in cabbage PLD assay is not significant, unpaired t test, n=4-5.

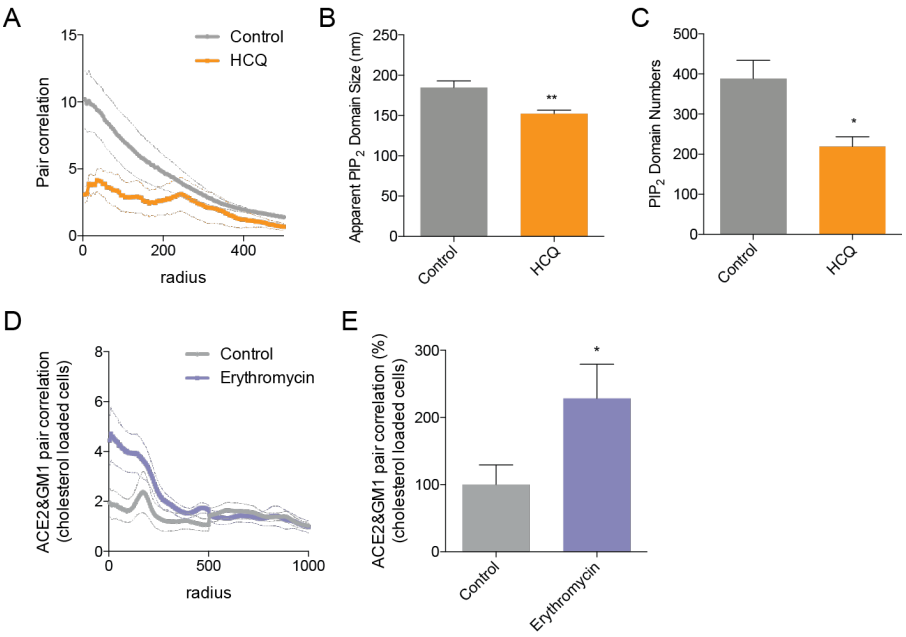

Fig. S3. dSTORM of PIP_2 domains. (**A**) Pair correlation analysis of dSTORM imaging (Fig. 3C). HCQ treatment decreased association of ACE2 and PIP_2. **(B-C)** Bar graph of the apparent raft diameter analyzed by DBSCAN cluster analysis. HCQ decreases both raft diameter (B) and number (C) of PIP_2 domains. Data are expressed as mean ± s.e.m., *P ≤ 0.05, **P ≤ 0.01, one-way ANOVA, n=5-6. **(D-E)** Pair correlation (D) and percent of pair correlation calculated at short distances (0-5 nm) (E) of dSTORM imaging. Erythromycin treatment decreased association of ACE2 with GM1 rafts. Data are expressed as mean ± s.e.m., *P ≤ 0.05, **P ≤ 0.01, unpaired t test, n=10.