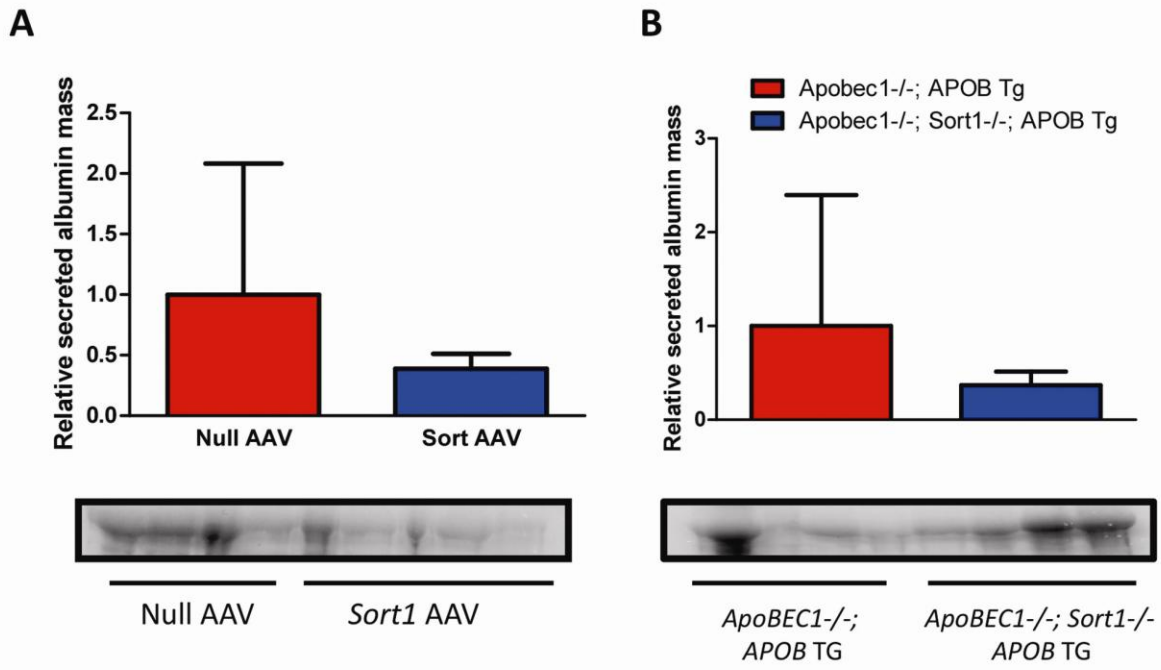
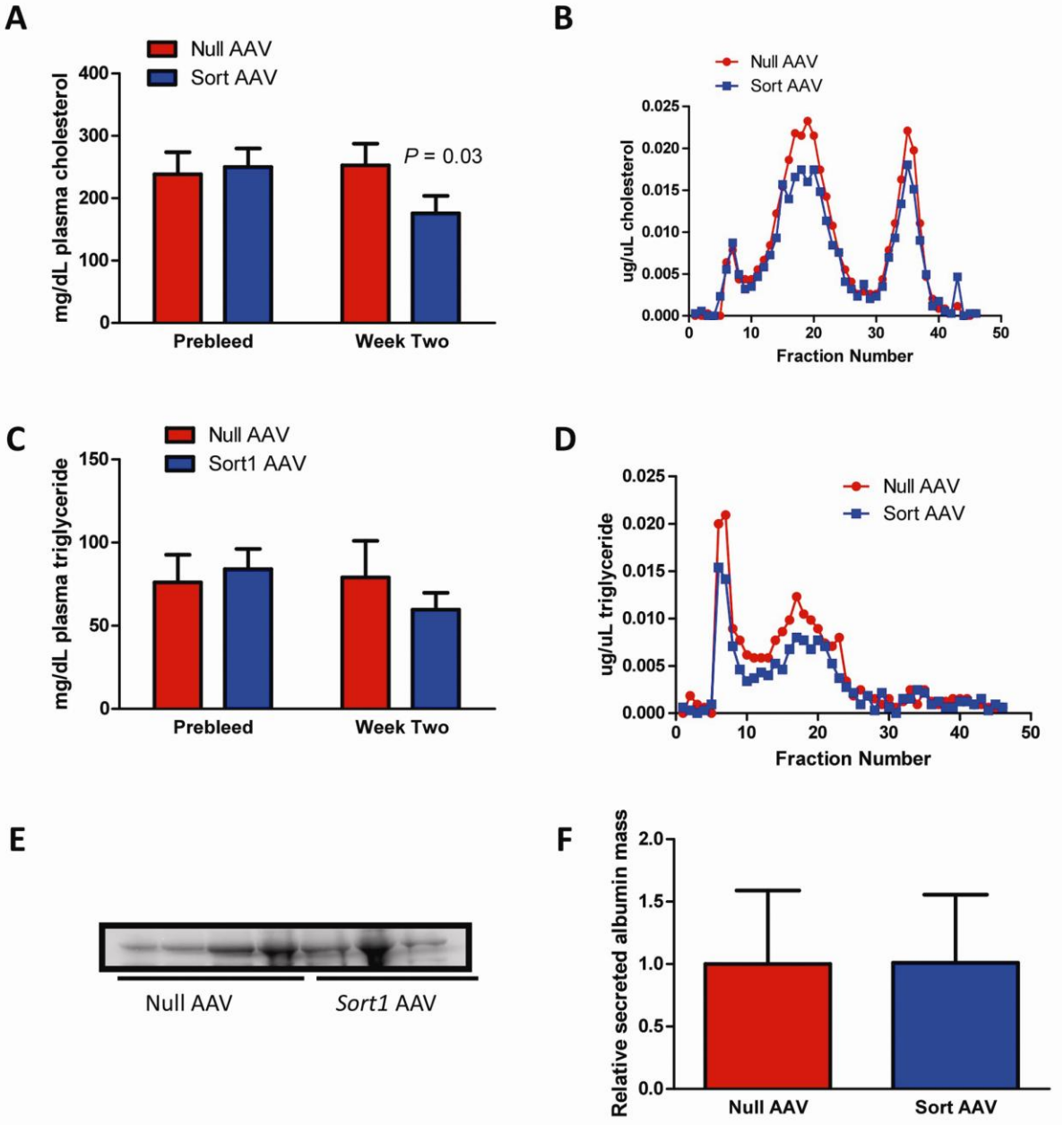
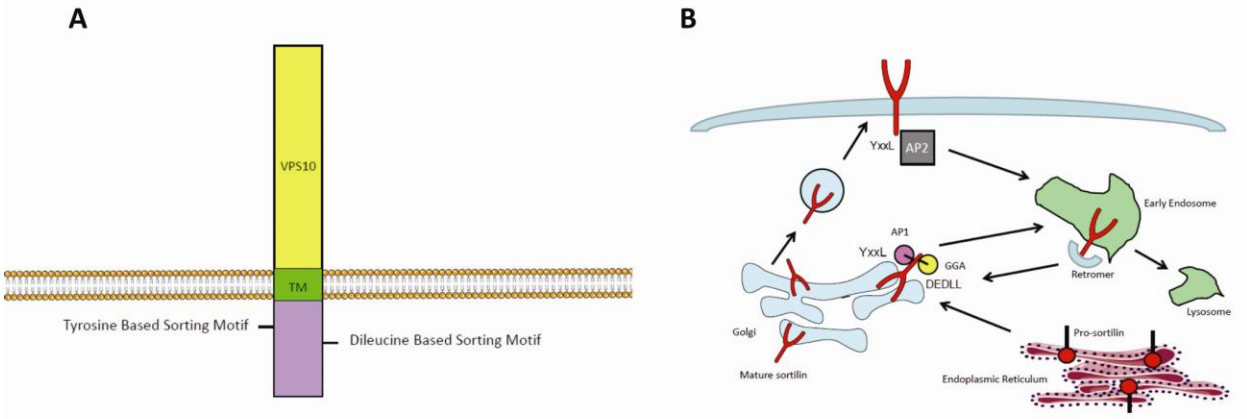


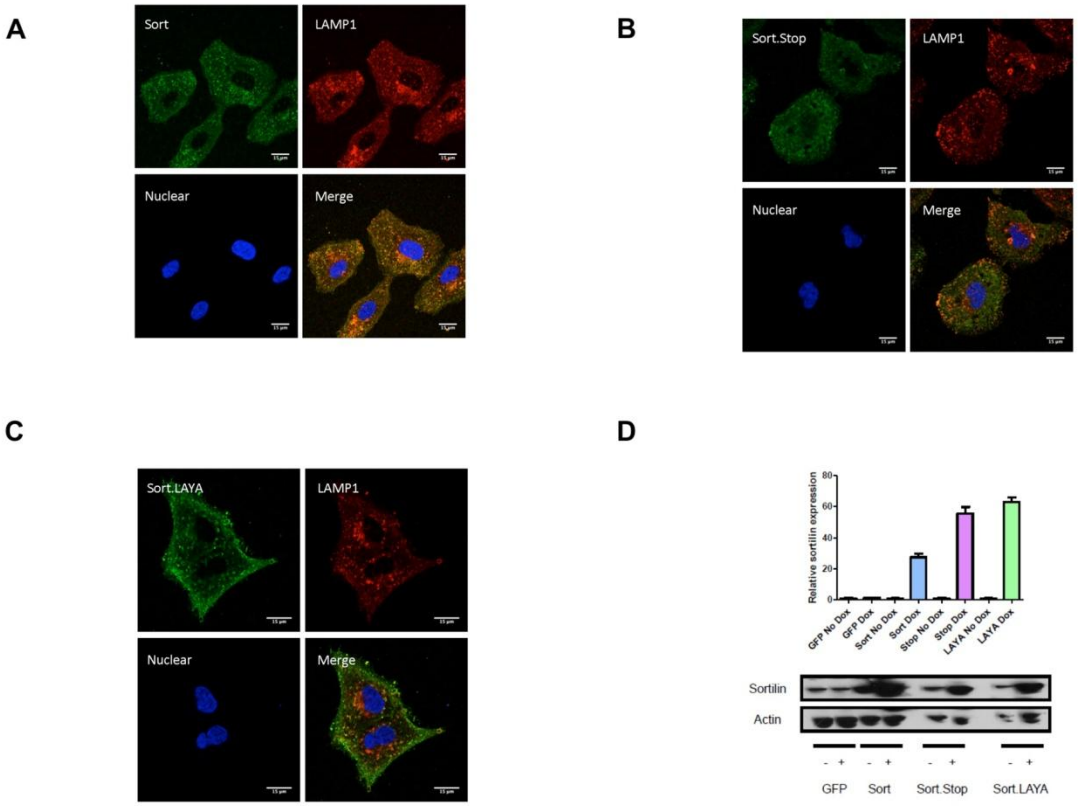
Supplementary Figure 1. Normalized albumin blots for *in vivo* secretion studies in **(A)** wild-type and **(B)** *Apobec1-/-; APOB* Tg mice (8-10 week old female mice). One hour plasma was run on an SDS gel and gels were dried and autoradiography was performed. Albumin autoradiographs and counts in the albumin bands were normalized to the 2 minute plasma counts.



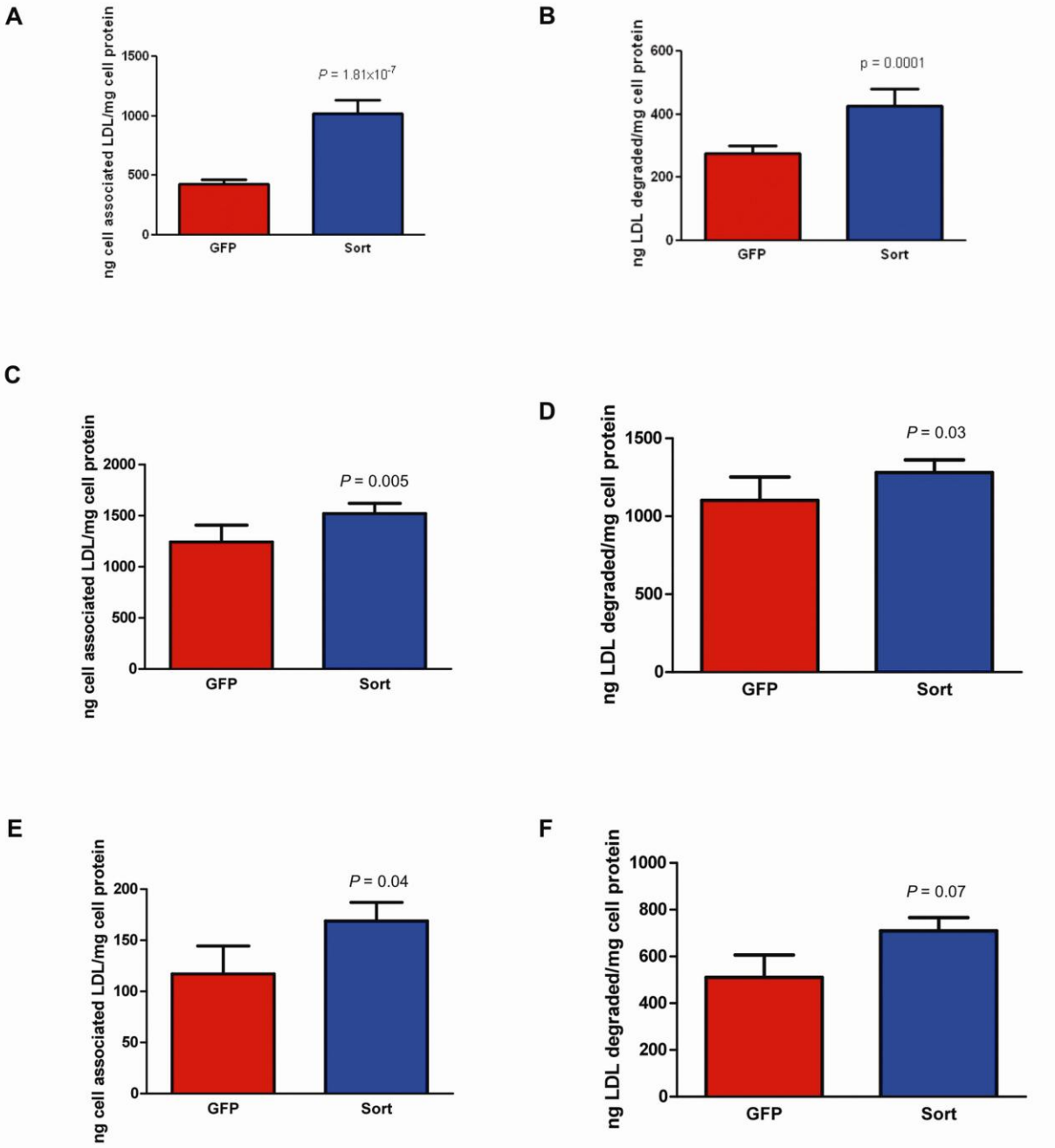
Supplementary Figure 2. *Sort1* expression in Ldlr-/- mice reduces plasma cholesterol.
8 *Ldlr-/-* mice (8-10 week old female mice) were fasted for four hours and blood was drawn by retro-orbital bleed and analyzed by **(A, C)** auto-analyzer and by **(B, D**) fast protein liquid chromatography. **(E, F)** Albumin autoradiographs and counts in the albumin bands normalized to the 2 minute plasma count for *in vivo* VLDL production studies in *Ldlr-/-* mice expressing *Sort1*.



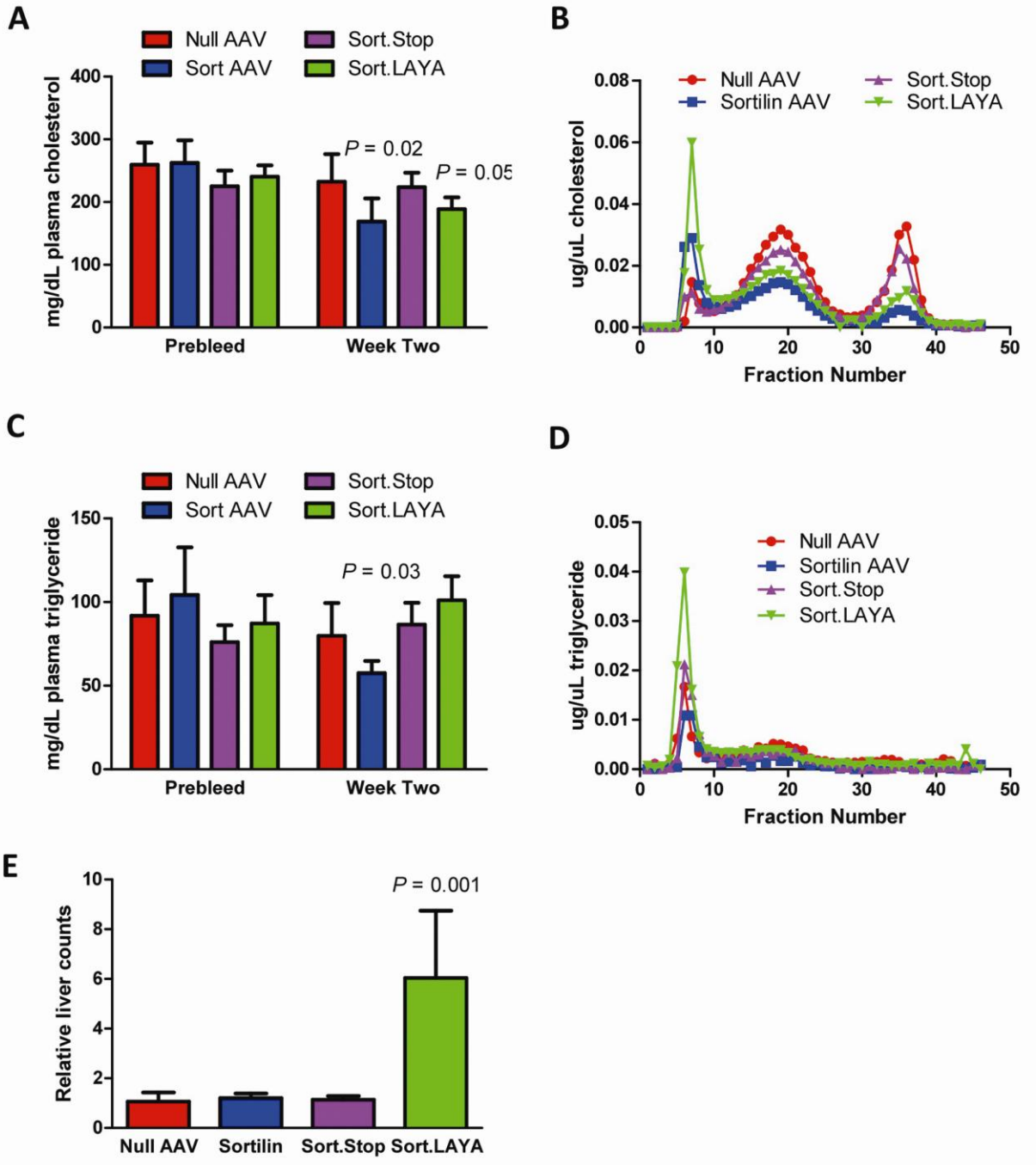
Supplementary Figure 3. **Schematic representation of the sortilin protein.**
(A) Sortilin has a luminal VPS10 domain for ligand binding and a cytoplasmic tail harboring two lysosomal sorting motifs, a tyrosine-based and a dileucine-based sorting motif **(B)** Sortilin is synthesized in the endoplasmic reticulum (ER) as a proprotein, which is incapable of binding ligands, and then is transported to the Golgi apparatus where it is cleaved by furin to generate the mature sortilin protein. From the Golgi apparatus, sortilin can go to the plasma membrane (~10%) or to the early endosome (~90%) At the cell surface, sortilin can bind extracellular ligands and bring them to the endolysosomal system by clathrin-dependent endocytosis. Sortilin is retrieved from the endolysosomal system by retromer and trafficked back to the Golgi. Golgi-localized sortilin can traffic to the early endosome and deliver ligands to the endolysosomal system, as well.



Supplementary Figure 4. **Sortilin trafficking mutants Sort.Stop and Sort.LAYA do not localize to the endolysosome system in HuH-7 cells.** HuH-7 cells were made that stably express wild-type sortilin, Sort.Stop or Sort.LAYA and sortilin localization was assessed by immunofluorescence **(A)** Wild-type sortilin colocalizes with the lysosome marker LAMP1 while **(B)** Sort.Stop localizes to an intracellular, non-lysosomal compartment and **(C)** Sort.LAYA localizes disproportionately to the plasma membrane and does not co-localize with LAMP1 **(D)** Real time PCR and immunoblot of sortilin demonstrating *Sort1* induction with dox treatment

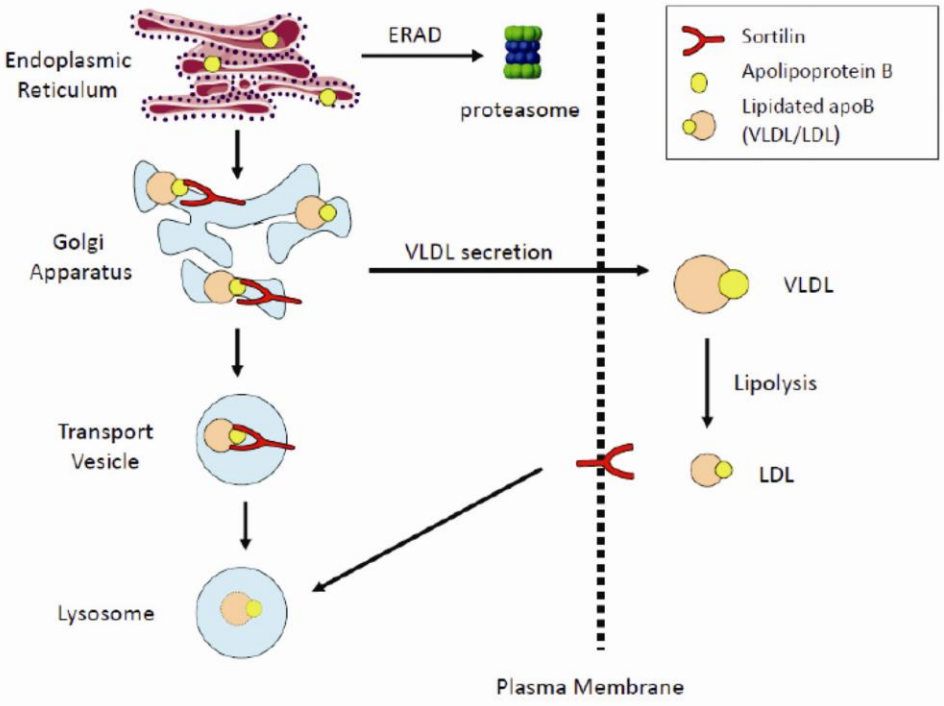


Supplementary Figure 5. *Sort1* expression increases LDL cell association and degradation in multiple cell types.
Cells were transfected with *Sort1* cDNA or GFP cDNA (control) and LDL cell association and degradation assays were performed **(A-B)** Expression of *Sort1* in 293T cells increases LDL cell association 2.3-fold and increases LDL degradation 2.5-fold **(C-D)** *Sort1* expression in CHO cells increases LDL cell association and degradation 1.2-fold **(E-F)** *Sort1* expression in ldlD cells increases LDL cell association and degradation 1.3-fold



Supplementary Figure 6. Expression of wild-type sortilin and Sort.LAYA reduces plasma cholesterol in *Ldlr-/-* mice, while Sort.Stop does not affect plasma cholesterol.

Ldlr-/- mice (8-10 week old females) were fasted for four hours and blood was drawn by retro-orbital bleed and plasma lipids were measured by **(A,C)** autoanalyzer and **(B,D)** fast protein liquid chromatography. Both wild-type sortilin and Sort.LAYA reduced total plasma cholesterol by 40%. **(E)** Mice were injected with $2x10^6$ counts of ^{125}I-LDL via tail vein. 24 hours after injection, animals were sacrificed and livers were harvested and counted. Liver counts were normalized to liver weight and total injected radioactivity. Mice expressing Sort.LAYA had a 6-fold increase in liver-associated ^{125}I-LDL counts.



Supplementary Figure 7. Proposed model of how sortilin expression reduces plasma LDL-C
apoB synthesis and lipidation begins in the Endoplasmic Reticulum (ER). When insufficient lipid is available to lipidate nascent apoB, apoB undergoes proteasome-mediated degradation (ERAD). Bulk lipid addition continues in the Golgi apparatus to form triglyceride-rich VLDL. Golgi localized apoB can be trafficked to the lysosome for degradation. Our data are consistent with a model in which sortilin serves as a sorting receptor that targets Golgi-localized apoB/VLDL to the lysosome for degradation. VLDL that does not undergo ER or Golgi associated degradation is secreted as VLDL and can be lipolyzed to generate LDL. Cell surface sortilin can bind LDL at the plasma membrane and traffic the LDL to the endolysosomal system for degradation.