Supporting Information:

Rational Targeting of Cellular Cholesterol in Diffuse Large B-Cell Lymphoma (DLBCL) Enabled by Functional Lipoprotein Nanoparticles: A Therapeutic Strategy Dependent on Cell of Origin

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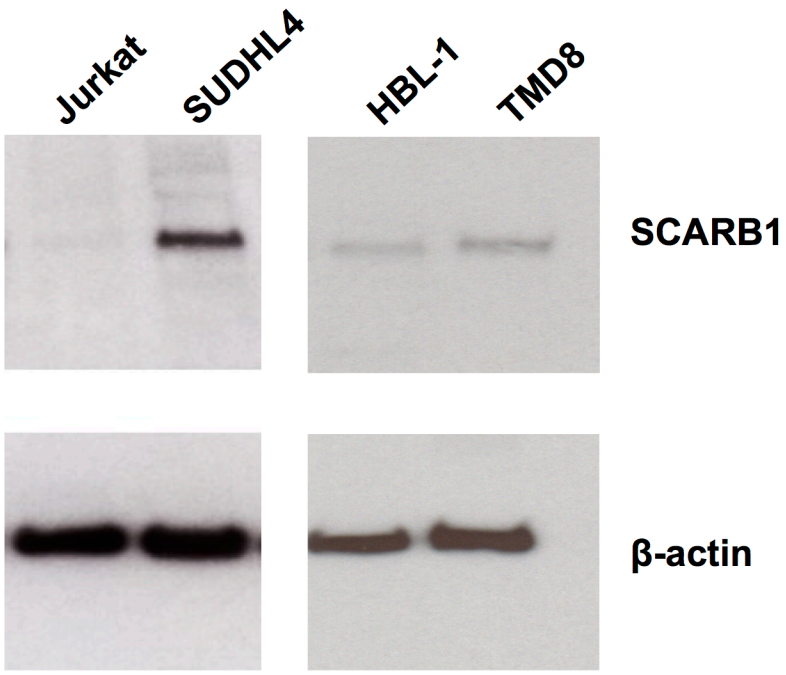
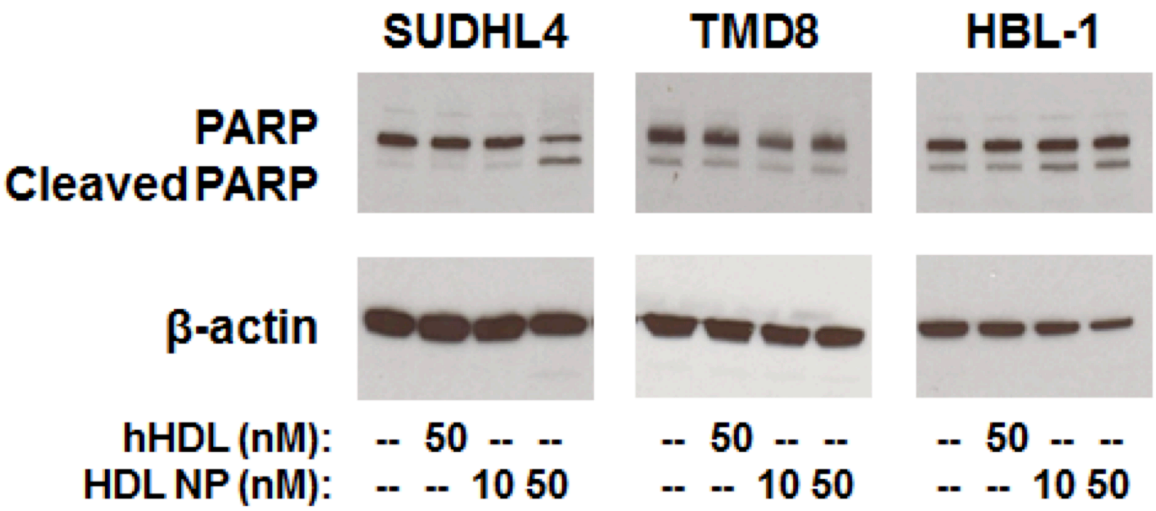
Total Number of Supplemental Figures and Tables: 13

Supplemental Figure S1



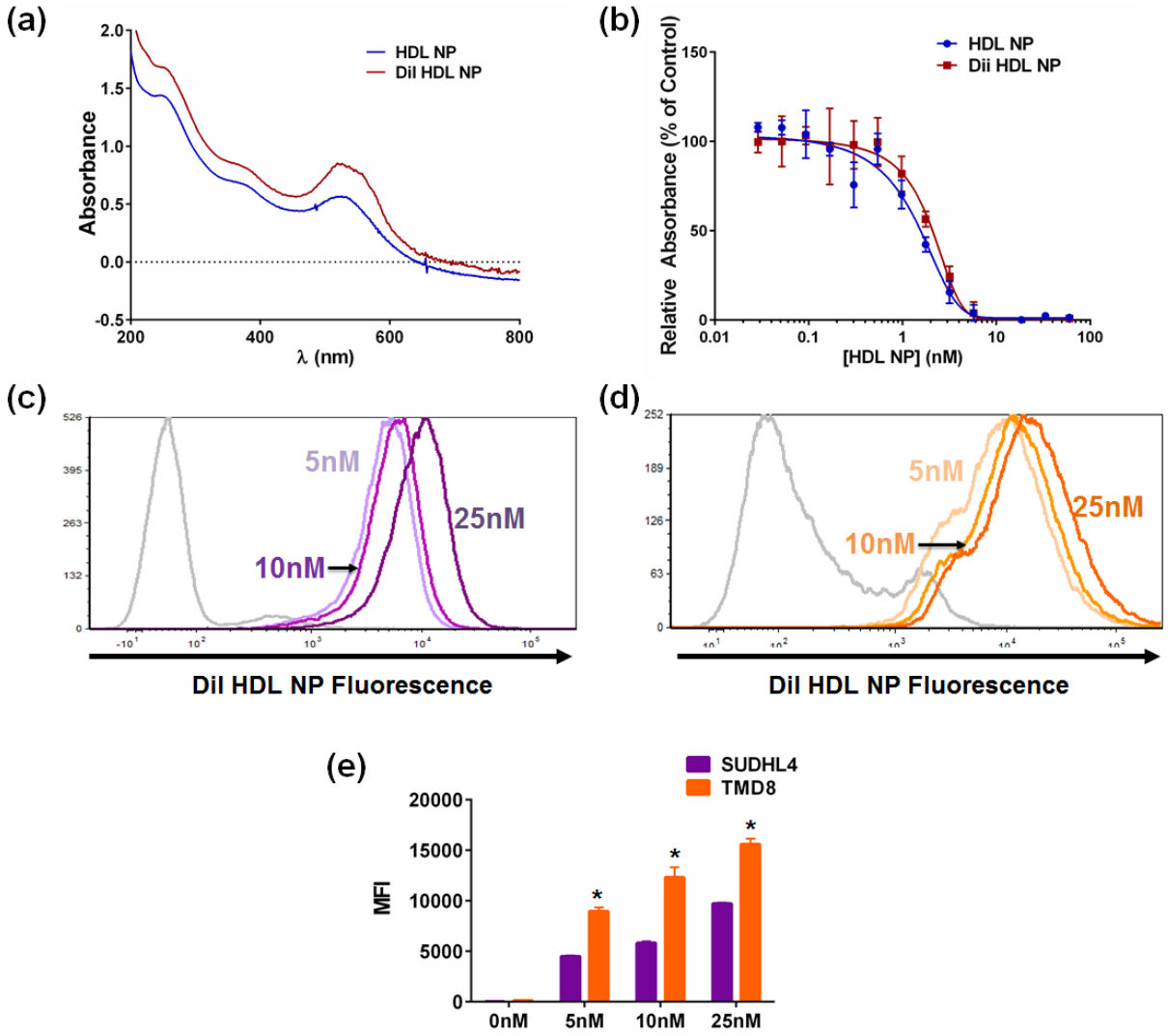
Supplemental Figure S1: NHL cell lines express SCARB1. Western blot of SUDHL4, TMD8, HBL-1 and Jurkat cell lines for the HDL receptor SCARB1.

Supplemental Figure S2



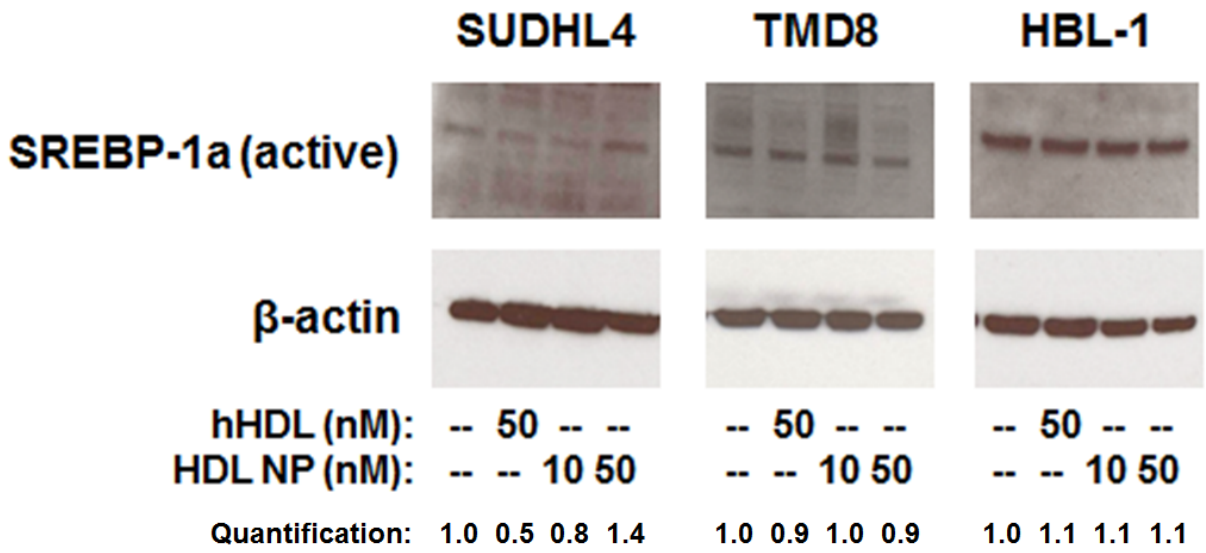
Supplemental Figure S2: HDL NPs induce PARP cleavage in GC DLBCL but not ABC DLBCL cell lines. HDL NPs induced PARP cleavage in the SUDHL4 cell line at 48 hrs of treatment, but not in TMD8 or HBL-1 cells.

Supplemental Figure S3



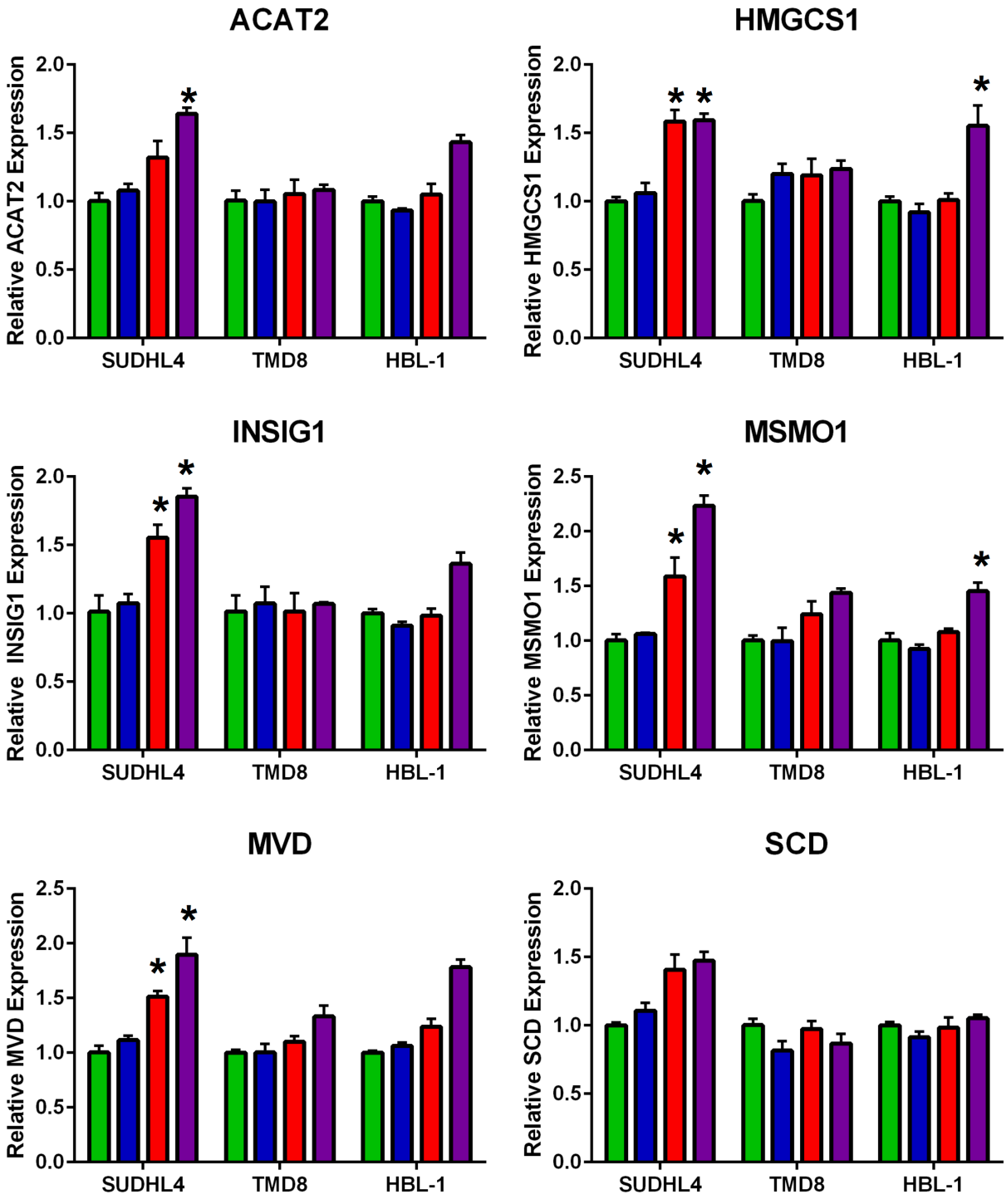
Supplemental Figure S3: DiI HDL NP characterization and uptake in DLBCL cells. (a) DiI HDL NPs have similar UV/Vis spectra compared to HDL NPs. (b) DiI HDL NPs induce GC DLBCL cell death similar to HDL NPs. (c-e) DiI HDL NP binding/ internalization in SUDHL4 and TMD8 cells treated with DiI HDL NPs for 24 hours. Representative histograms for SUDHL4 (c) and TMD8 (d) cells treated with increasing concentrations of DiI HDL NPs. (e) Median fluorescent intensities of DiI HDL NP-treated SUDHL4 and TMD8 cells. *p<0.0001 vs. SUDHL4.

Supplemental Figure S4



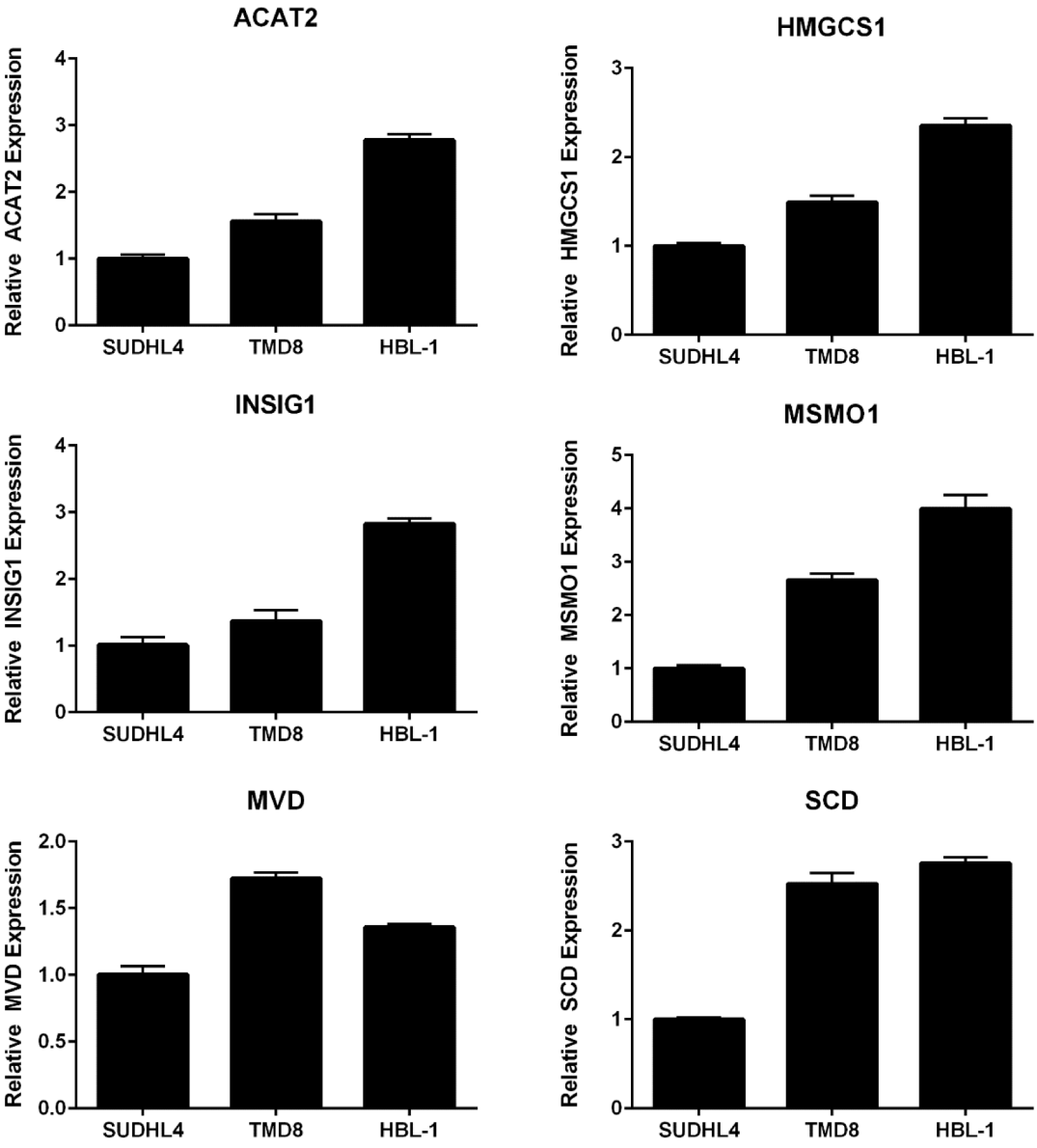
Supplemental Figure S4: HDL NPs activate SREBP-1a in SUDHL4 but not TMD8 and HBL-1 cells. Western blot analysis of SREBP-1a in SUDHL4, TMD8 and HBL-1 cells treated with HDL NPs (10nM, 50nM), human HDL (hHDL, 50nM) or PBS for 48 hours. β-actin was used as a loading control.

Supplemental Figure S5



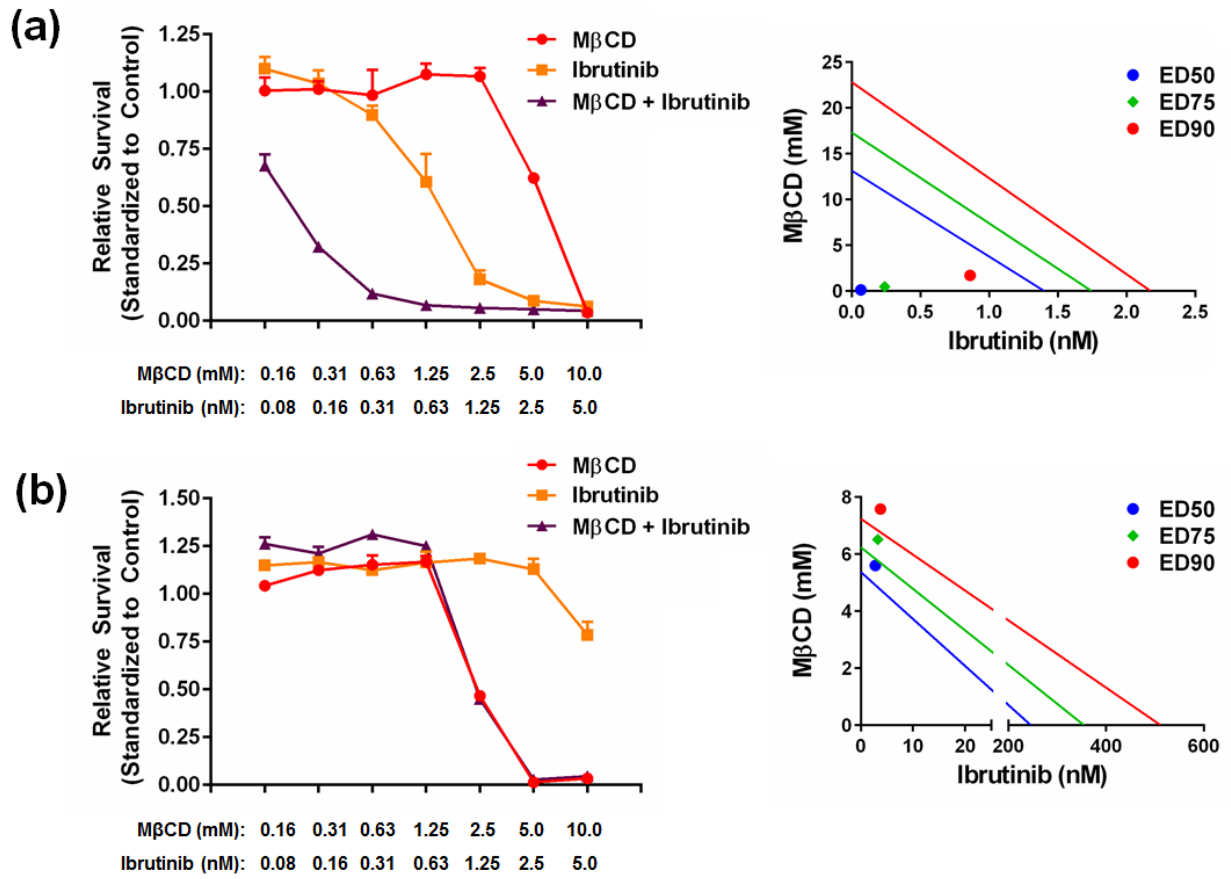
Supplemental Figure S5: HDL NPs upregulate cholesterol biosynthesis genes. RT-qPCR analyses of 6 prominent cholesterol synthesis genes. HDL NPs increased cholesterol biosynthesis gene expression in GC DLBCL cell lines vs. ABC DLBCL.

Supplemental Figure S6



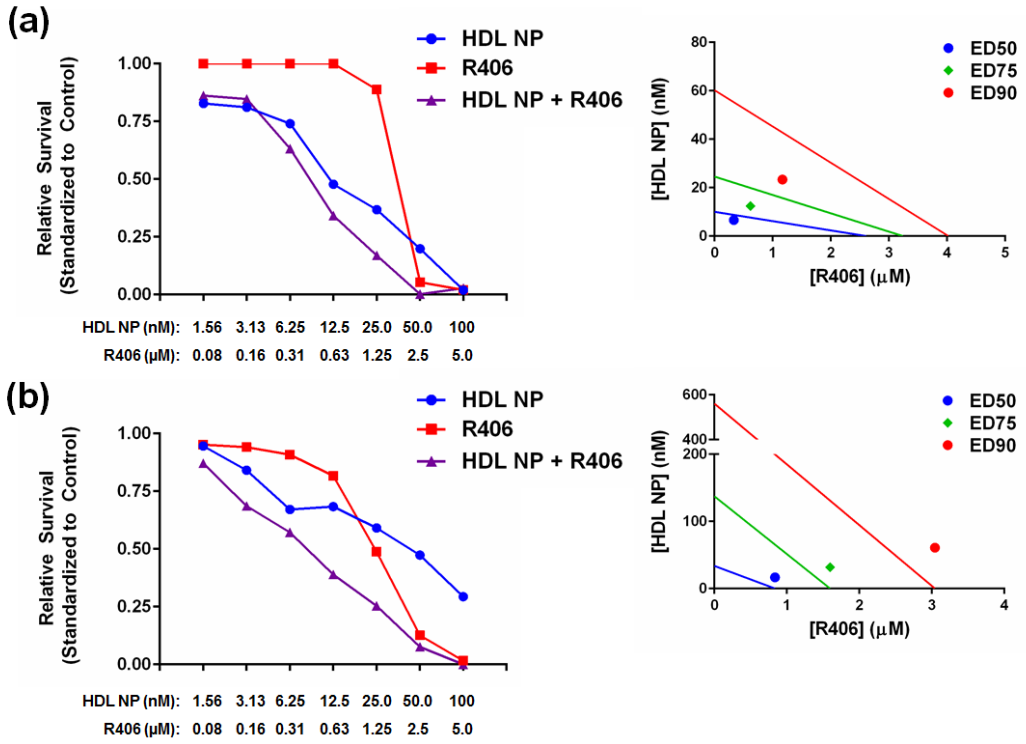
Supplemental Figure S6: Cholesterol biosynthesis genes are expressed at a higher level in ABC compared to GC DLBCL. RT-qPCR for cholesterol biosynthesis genes. Data were analyzed using the ΔΔCt method as relative to expression in SUDHL4.

Supplemental Figure S7



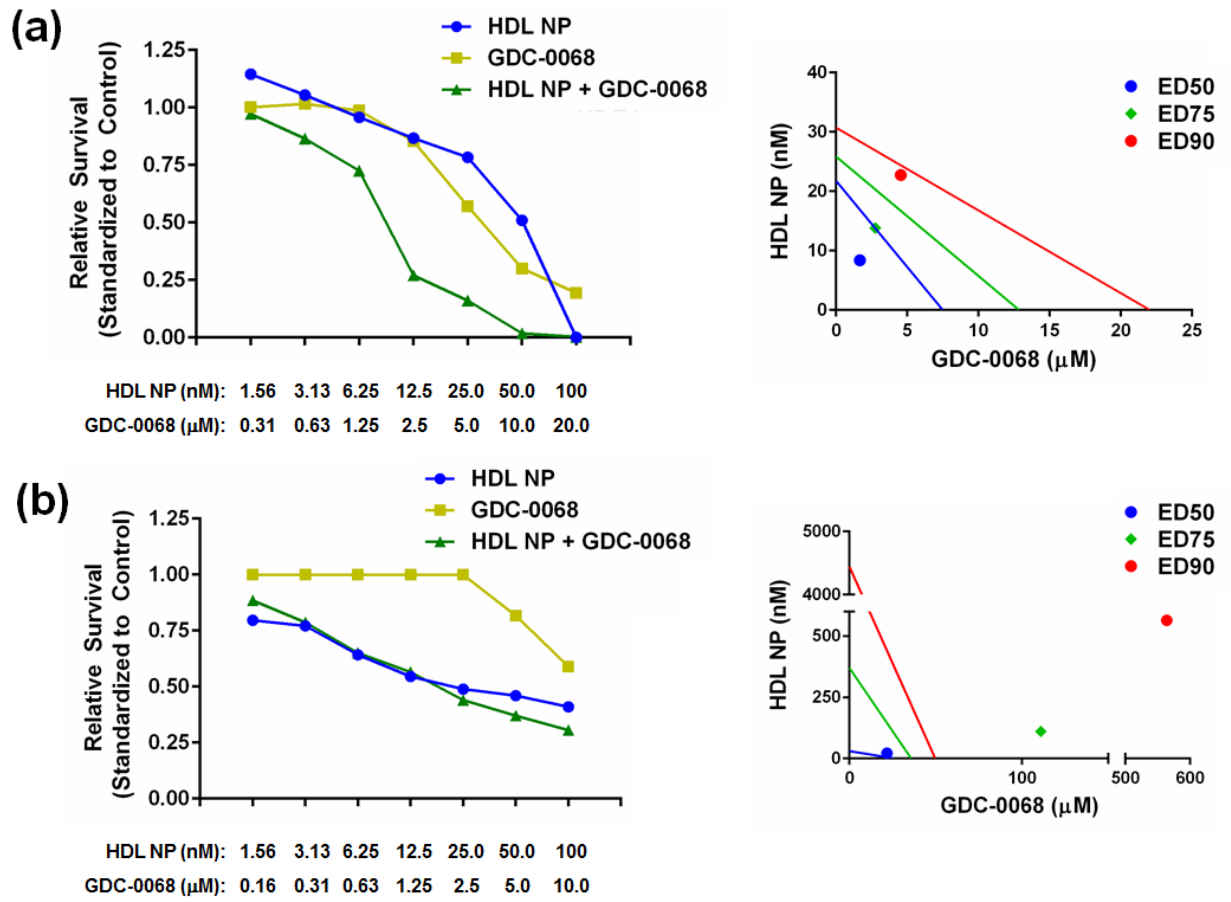
Supplemental Figure S7: MβCD synergizes with ibrutinib in TMD8 cells but not in HBL-1 cells. TMD8 (A) and HBL-1 (B) cells were treated with MβCD, ibrutinib or a combination and cell death assayed at 72 hours. Left- dose response curves. Right- Isobologram depicting synergy at the ED50 (blue), ED75 (green) and ED90 (red) levels.

Supplemental Figure S8



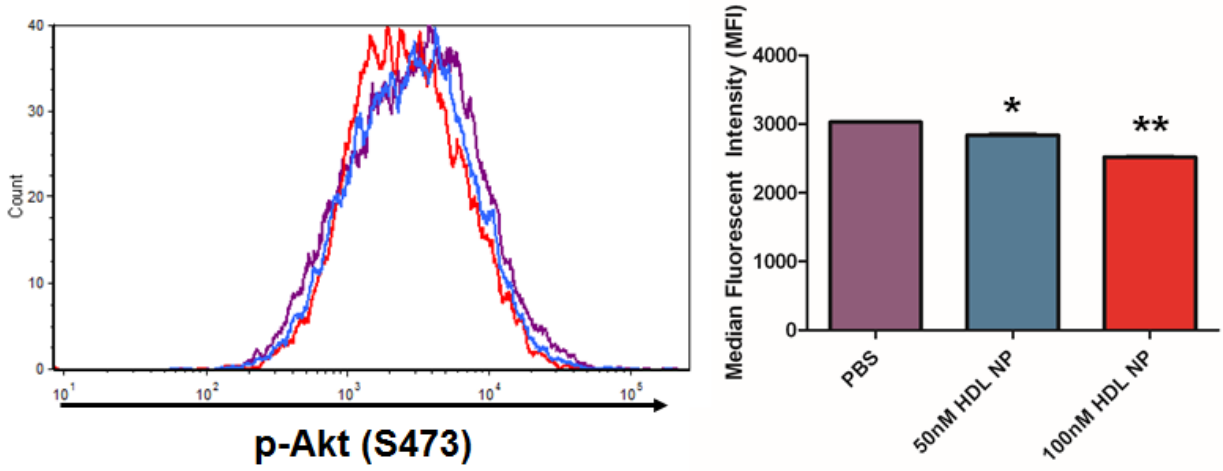
Supplemental Figure S8: HDL NPs synergize with R406 in TMD8 cells but not in HBL-1 cells. TMD8 (A) and HBL-1 (B) cells were treated with HDL NPs, R406 or a combination and cell death assayed at 72 hours. Left- dose response curves. Right- Isobologram depicting synergy at the ED50 (blue), ED75 (green) and ED90 (red) levels.

Supplemental Figure S9



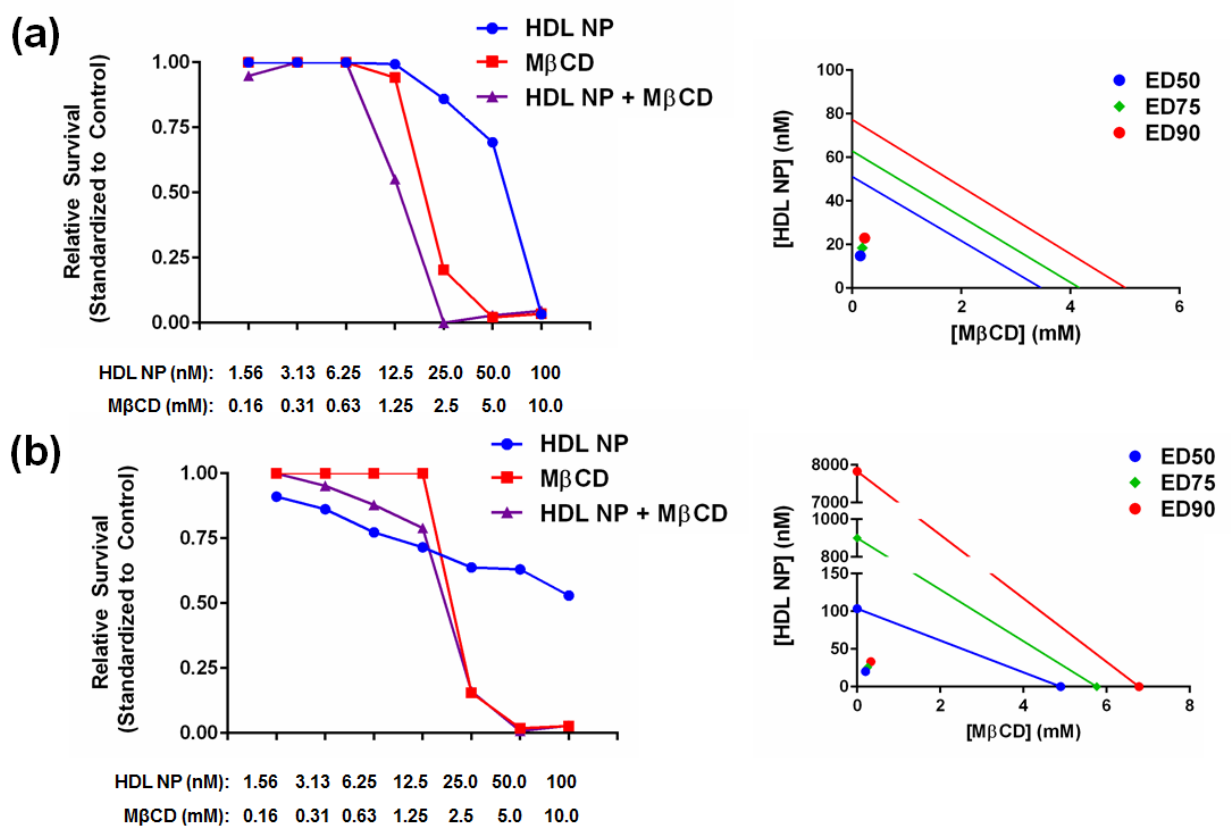
Supplemental Figure S9: HDL NPs synergize with the AKT inhibitor GDC-0068 in TMD8 but not HBL-1 cells. TMD8 (A) and HBL-1 (B) cells were treated with HDL NPs, GDC-0068 or a combination and cell death assayed at 72 hours. Left- dose response curves. Right- Isobologram depicting synergy at the ED50 (blue), ED75 (green) and ED90 (red) levels.

Supplemental Figure S10



Supplemental Figure S10: Phos-flow analysis of p-AKT in TMD8 cells. TMD8 cells were exposed to HDL NPs for 2 hours prior to staining and flow cytometric analysis. N=3 for each condition. *p<0.05 vs. PBS control by 1-way ANOVA. **p<0.05 vs. PBS and 50nM HDL NP by 1-way ANOVA. All data are presented as mean ± s.e.m.

Supplemental Figure S11



Supplemental Figure S11: MβCD synergizes with HDL NPs against TMD8 and HBL-1 cells. TMD8 (A) and HBL-1 (B) cells were treated with HDL NPs, MβCD or a combination and cell death assayed at 72 hours. Left- dose response curves. Right- Isobologram depicting synergy at the ED50 (blue), ED75 (green) and ED90 (red) levels.

Supplemental Table S1: Combinatorial indices for HDL NPs and small molecule inhibitors in TMD8 and HBL-1 cell lines.

		Combination Index (CI) at		
Cell Line	**Drug Combination**	**ED50**	**ED75**	**ED90**
TMD8	HDL NP + GDC-0068 (1:200)	0.60789	0.50931	0.43209
	HDL NP + Pilaralisib (1:100)	1.26515	1.74498	2.40848
	HDL NP + Ibrutinib (20:1)	0.6754	0.71867	0.76472
	HDL NP + R406 (1:50)	0.78572	0.69772	0.67877
	HDL NP + MβCD (1:10,000)	0.33117	0.33272	0.3435
	Ibrutinib + MβCD (1:2,000,000)	0.05802	0.16535	0.47144
HBL-1	HDL NP + GDC-0068 (1:1000)	1.55559	3.39827	11.47275
	HDL NP + Pilaralisib (1:1000)	2.08512	4.00031	8.75754
	HDL NP + Ibrutinib (20:1)	0.31988	0.11876	0.06326
	HDL NP + R406 (1:50)	1.49728	1.23243	1.10864
	HDL NP + MβCD (1:10,000)	0.23642	0.07385	0.05341
	Ibrutinib + MβCD (1:2,000,000)	1.05307	1.05331	1.05399

Supplemental Table S2: Blood chemistry parameters of SUDHL4 tumor xenograft bearing mice following treatment.

	Saline	**HDL NP 3x/ week**	**HDL NP 5x/ week**
RBC (106 cells/ul)	9.51 ± 0.09	9.55 ± 0.14	9.51 ± 0.13
HGB (g/L)	14.54 ± 0.12	14.29 ± 0.18	14.10 ± 0.20
HCT (% blood volume)	48.87 ± 0.43	48.59 ± 0.69	47.89 ± 0.70
PLT (x10^3 cells/µl)	1039.7 ± 18.78	1079.3 ± 30.4	1121.3 ± 52.7
HDL (mg/dL)	49.89 ± 2.21	43.0 ± 0.0	37.44 ± 6.87
LDL (mg/dL)	7 ± 0	7 ± 0	6 ± 1
ALT (U/L)	29.25 ± 2.14	27.20 ± 5.84	25.71 ± 7.41
AST (U/L)	69.4 ± 6.18	70.7 ± 4.43	61.7 ± 12.9
BUN (mg/dL)	20.0 ± 1.32	17.60 ± 1.0	15.14 ± 3.35