Supporting Information

Core Hydrophobicity Tuning of a Self-Assembled Particle Results in Efficient Lipid Reduction and Favorable Organ Distribution

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Materials and Instrumentations. All chemicals were received and used without further purification unless otherwise noted. PLGA-COOH of inherent viscosity of 0.15-0.25 dL/g was purchased from Lactel. Cholesteryl oleate (CO) and nitric acid were purchased from Sigma-Aldrich. NBD-cholesterol, QDot 705 ITK amino PEG-QDs, and AmplexRed cholesterol quantification kit were purchased from Invitrogen. The apoA-I mimetic peptide L-4F peptide Ac-FAEKFKEAVKDYFAKFWD-COOH was custom synthesized by RS Synthesis Inc. and characterized by MALDI and HPLC. Carboxylic acid 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000] (DSPE-PEG-COOH) was purchased from Avanti Polar Lipids, Inc. Stearyl triphenylphosphonium bromide (Stearyl-TPP) and PLGA-PEG-QDs were synthesized according to methods previously described by us.[1] Polyvinyl alcohol (PVA) (86-89% hydrolyzed) of low molecular weight (average molecular weight of 10,000 to 26,000) was purchased from Alfa Aesar. AdipoRed was purchased from Lonza. Ultrapure lipopolysaccharide (LPS) from *E. coli* was purchased from InvivoGen. Native HDL from human plasma (BT-914) was purchased from Biomedical Technologies. Lipoprotein deficient fetal bovine serum (FBS) (RP-056) and modified human lipoprotein oxidized LDL (RP-047) were obtained from Intracell. Oligomycin, rotenone, antimycin-A, and trifluorocarbonylcyanide phenylhydrazone (FCCP) were purchased from Sigma Aldrich. Anti-alpha smooth muscle Actin antibody (ab5694) and goat anti-rabbit - H&L (Alexa Fluor® 488) polyclonal secondary antibody (ab150077) were procured from Abcam. Mice study cytokines were measured using mouse ELISA kits from BD sciences Inc. (catalog no. IL-6: BDB 555240, TNF-α: BDB 558534, IL-10: BDB 555252, IL-1β: BDB 557953, MCP-1: BDB 555260).

Reactive oxygen species (ROS) was measured using 2′,7′-dichlorofluorescin diacetate (DCFDA, Cat# D6883) procured from sigma.

Distilled water was purified by passage through a Millipore Milli-Q Biocel water purification system (18.2 MΩ) containing a 0.22 μm filter. Cells were counted using Countess® Automated cell counter procured from Invitrogen. Dynamic light scattering (DLS) measurements were carried out using a Malvern Zetasizer Nano ZS system. Optical measurements were carried out on a NanoDrop 2000 spectrophotometer. Transmission electron microscopy (TEM) images were acquired using a Philips/FEI Tecnai 20 microscope. Inductively coupled plasma mass spectrometry (ICP-MS) studies were performed on Agilent 7900 ICP-MS instrument. Plate reader analyses were performed on a Bio-Tek Synergy HT microplate reader. Bioenergetic assays were carried out using Agilent Seahorse XF^e96 analyzer. Confocal imaging on cells was performed on a on a Leica TCS SP5 confocal microscope. Clinical chemistry analyses were performed at UGA College of Veterinary Medicine using a Hitachi P-module biochemical analyzer.

Synthesis of Stearyl-TPP. Stearyl-TPP was synthesized and characterized by following methods previously reported by us.[1]

Synthesis of Library of T-HDL-NPs and NT-HDL-NPs with Varied CO Feed. T-HDL-NPs were prepared *via* self-assembly of PLGA-COOH, CO, stearyl-TPP, DSPE-PEG-COOH, and apoA-I mimetic L-4F peptide through a modified nanoprecipitation. PLGA-COOH (10 to 90 μL, 25 mg/mL in CH_3CN), CO (90 to 10 μL, 25 mg/mL in dimethyl sulfoxide/tetrahydrofuran=9:1) were mixed so that the total volume of PLGA and CO was 100 μL. Stearyl-TPP (5 mg/mL, 100 μL) and DSPE-PEG-COOH (1 mg/mL, 100 μL) with a weight ratio of 16% to the PLGA polymer were dissolved in 4% ethanol aqueous

solution. To prepare the library of NT-HDL-NPs, PVA (5 mg/mL in 4% aqueous ethanol, 100 μL) was used instead of stearyl-TPP during the modified nanoprecipitation process. The lipid solution was heated to 65 °C to ensure all lipids are in the non-assembled state. The PLGA/CO solution was added into the preheated lipid solution drop-wise under vigorous stirring. The mixed solution was vortexed vigorously for 3 min followed by vigorous stirring for 2 h at room temperature. The remaining organic solvent and free molecules were removed by washing the NP solution three times using an Amicon Ultra-4 centrifugal filter with a molecular weight cutoff of 100,000 Da. The NPs were incubated with apoA-I mimetic L-4F peptide (1 mg/mL, 50 μL) at 4 °C for 12-14 h. The NPs were further washed three times using Amicon Ultra-4 centrifugal filter with a molecular weight cutoff of 100,000 Da to removed unbound peptide. NP size (diameter, nm), PDI, and surface charge (zeta potential, mV) were obtained from three independent measurements. For TEM studies, NP solution was diluted with water, and then 4% uranyl acetate was added into the solution to stain the NPs. This mixture was vortexed for few sec and dropped into a copper grid with overnight drying at room temperature. TEM images were recorded on FEI Tecnai20 transmission electron microscope operating at 200 kV. QD loading in the NPs was quantified by ICP-MS.

Quantification of CO in NPs. Cholesterol content of NPs was quantified by AmplexRed cholesterol quantification kit (purchased from Invitrogen, Cat. No. A12216). NP or CO standard solutions (50 μL) were incubated with a working reagent solution composed of AmplexRed (300 μM), horse radish peroxidase (HRP) (0.2 U/mL), cholesterol oxidase (2 U/mL), and cholesterol esterase (0.2 U/mL) for 30 min at 37 °C in the dark. The fluorescence was measured using a plate reader at an excitation of 530 nm and an

emission of 590 nm. Relative fluorescence units (RFUs) were converted to cholesterol concentration using a standard curve for cholesteryl oleate.

Loading and Encapsulation Efficiency (EE) Calculations. %Loading and %EE of CO was calculated using following formulas.

%Loading of CO = 100 X Weight of CO in NP/Total weight of NP

%EE of CO = 100 X Weight of CO in NP /Feed weight of CO

NBD-Cholesterol Binding Studies. Cholesterol binding to T-HDL-NPs, NT-HDL-NPs, and hHDL was determined by adding 0.025 mg/mL of NPs into varying concentrations of NBD-cholesterol (0, 0.00078, 0.00156, 0.00312, 0.00625, 0.0125, 0.025 mg/mL) in water. The solutions were vortexed and incubated for 5 min, 30 min, 1 h, 6 h, and 24 h. The fluorescence was quantified by plate reader with an excitation wavelength 473 nm and emission of 560 nm.

MitoStress Test on Cardiomyocytes. Prior to the assay, XF^e96 sensor cartridges were hydrated. To each well of an XFe96 utility plate, 200 μL of Seahorse Bioscience calibrant was added and the XFe96 sensor cartridges were placed on top of the utility plate, and kept at 37 °C incubator without CO_2 for a minimum of 12 h. H9C2 rat cardiomyocytes were cultured in XFe96-well cell culture microplates (Seahorse Bioscience) at a density of 2×10^4 cells per well (0.10^6 cm^2) in 100 μL growth medium and then incubated for 24 h at 37 °C under 5% CO_2 atmosphere. After the cells were adhered, the cells were treated with T/NT-CO_{40}-HDL-NP (20 or 50 μg/mL with respect to total NP) or T/NT-CO_{70}-HDL-NP (20 or 50 μg/mL with respect to total NP) for 4 h at 37 °C under 5% CO_2 atmosphere. After 4 h, all but 20 μL of the culture medium was removed from each well and the cells were rinsed three times with 180 μL of XF stress test optimization medium supplemented

with sodium pyruvate, L-glutamine, and D-glucose and pre-warmed to 37 °C, and finally 180 μL of the optimization medium was added to each well and the plate was incubated at 37 °C without CO_2 for 1 h prior to assay. The OCR was measured simultaneously for 16 min to establish a baseline rate. Different parameters of respiration, basal respiration, coupling efficiency, and spare respiratory capacity, were investigated by using a Seahorse XFe96 cell Mito Stress Test Kit. The different parameters of respiration were calculated by subtracting the average respiration rates before and after the addition of the electron transport inhibitors oligomycin (1.0 μM) and FCCP (1.0 μM), an ionophore that is a mobile ion carrier, and a mixture of antimycin-A (1.0 μM) (which is a complex III inhibitor) and rotenone (1.0 μM), a mitochondrial inhibitor that prevents the transfer of electrons from the Fe–S center in complex I to ubiquinone. Test articles on each well had four replicates.

Macrophage Derived Foam Cell Formation and Prevention by NPs. RAW macrophages were plated on a 24-well plate at a density of $2.0x10^6$/well in RPMI and allowed to grow to confluency. The media was removed and a lipid depleted DMEM (10% lipoprotein deficient FBS, 1% penicillin-streptomycin) media was added and the cells were grown for an additional 24 h. For preventative treatment, T-CO_{40}-HDL-NPs, T-CO_{70}-HDL-NPs, or hHDL (0.1 mg/mL) were added and allowed to internalize for 6 h. The media was changed and fresh RPMI was added supplemented with oxidized LDL (Ox-LDL) (100 μg/mL). The cells were further incubated for 24 h. For therapeutic foam cell treatment, after 24 h treatment with lipid deprived media, the media was replaced with RPMI supplement with Ox-LDL (100 μg/mL) and the cells were incubated for 12 h. After which, the media was removed and NPs (T-CO_{40}-HDL-NPs, T-CO_{70}-HDL-NPs) or hHDL (0.1

mg/mL) were added and allowed to internalize for 24 h. The media was removed for both cases, and washed with 1x PBS (3x). To image the foam cells, AdipoRed in PBS was added to each well and incubated for 10 min. The AdipoRed was removed and the cells were washed with 1x PBS (5x). The plates were then either read on the plate reader for the relative fluorescent units or imaged *via* confocal microscopy (TRITC, 500 ms).

ROS Detection in Foam Cells. RAW 264.7 macrophages were plated on a 24 well plate at a density of 2.0×10^6 cells/well in RPMI and allowed to grow to confluency. The media was removed and lipid depleted DMEM (10% lipoprotein deficient FBS, 1% penicillin-streptomycin) media was added and the cells were grown for an additional 24 h. The media was changed and fresh RPMI was added supplemented with Ox-LDL (100 μg/mL). The cells were further incubated for 24 h. After which, the media was removed and T-CO_{40}-HDL-NPs or T-CO_{70}-HDL-NPs or hHDL (0.1 mg/mL) were added and allowed to internalize for 24 h. After which, a dichlorodihydrofluoroscein diacetate (DCFH-DA) solution in RPMI was added and incubated for 30 min at room temperature in the dark. The media was removed and the cells were then homogenized using DMSO. The cell lysates (50 μL) were then transferred to a 96 well plate and the fluorescence was measured on the plate reader (480 nm excitation, 530 nm emission).

Immunostaining of *α*-smooth Muscle Actin. Smooth muscle cells were plated at a cell density of 20,000 cells per well on glass coverslips placed in a 12-well plate and were allowed to adhere on the coverslips for overnight. Media was removed from the wells and the cells were then fixed with 4% paraformaldehyde for 15 min at room temperature and permeabilized using 0.2% Triton-X for 10 min. Cells were washed with 1X PBS for 3 times and blocked with 10% goat serum in 1X PBS for 6 h. Cells were washed thrice with 1X

PBS and treated with primary antibody in 10% goat serum containing 1X PBS for 12 h at 4 °C. After washing the cells for three more times with 1X PBS, secondary antibody was added and incubated for 2 h. Cells were finally washed three more times with 1X PBS and mounted on glass slides with DAPI containing mounting solution and imaged under confocal microscope.

Cholesterol Efflux Assay Using Macrophages and Aortic SMCs. Macrophage RAW 264.7 cells (40 000 cells/well) cells were plated in 96-well plate and grown for overnight. The medium was removed and cells were treated with NBD-cholesterol (5 μM) in DMEM containing 0.2% FBS and incubated for 5 h. The cholesterol labelled cells were then washed with 1XPBS (3 times) and T/NT-HDL-NPs (50 μg/mL) or human-HDL (100 μg/mL) was added to the cells and incubated for 2 h in the DMEM without serum and phenol red. The supernatant was transferred to another 96-well plate. The cell monolayers were solubilized using RIPA buffer with shaking for 30 min at room temperature. The fluorescence of supernatant and cell lysates was measured at 469/538 nm. The ratio of present in the media to that retained by the cells gave a measure of cholesterol efflux property of the NPs. Human HDL nanoparticle was used as a control. As for smooth muscle cells, 20,000 cells/well were plated and DMEM/F12 medium was used instead of DMEM.

Biodistribution and Lipid Reduction properties of Self Therapeutic NPs in Normal Mice. BALB/c white albino male mice age of 4 weeks were purchased from Jackson Laboratory, Bar Harbor, ME., and animal work was performed under aseptic condition. Quantum dot loaded T/NT-$CO_{40/70}$-HDL-NPs were injected at a dose of 10 mg/kg with respect to total construct. The animals regained consciousness soon after the injection

was completed and change in behavior such as dizziness and irritation was observed. An increase in pulse rate was also observed for 20-30 min. After half an hour improvement in behavior was observed and all the animals returned to their normal behavior. After 24 h of the administration time, surgery was performed under aseptic condition and blood was collected through cardiac puncture. The serum was isolated through centrifugation process (2400 rpm for 20 min) and lipid analysis was performed. Organs were harvested and ICP-MS analysis was done on the dissolved organ samples for biodistribution study. The total triglyceride (TG) in the serum was quantified by triglyceride quantification fluorometric assay kit from Abcam Inc. (Cat. No. ab65336). Specifically, the triglyceride standard (0-10 μM) was used to generate a standard curve. A 50 μL diluted serum sample (diluted with the buffer solution provided with the assay kit) and triglyceride standard samples were added into 96-well plate. Then, to each well, 2 μL lipase solution was added, followed by addition of 50 μL reaction mixture prepared by mixing 952 μL triglyceride assay buffer, 8 μL triglyceride probe, and 40 μL triglyceride enzyme mix. The reaction was incubated for 60 min at room temperature in the dark. Finally, the fluorescence was measured by using excitation at 530 nm and emission at 590 nm. The standard curve was used to determine triglyceride concentration in the serum samples. Serum cholesterol concentration was quantified by Amplex Red cholesterol quantification kit. The cholesterol reference standard provided by the Life Technologies Inc. with the kit was used to create a standard curve. The isolated serum samples (50 μL) were incubated with a working reagent solution (50 μL) composed of Amplex Red (300 μM), horseradish peroxidase (2 U/mL), cholesterol oxidase (2 U/mL), and cholesterol esterase (0.2 U/mL) for 1 h at 37 °C in the dark. This working agent was constructed by adding 75 μL of Amplex

Red reagent stock solution (20 mM), 50 μL horseradish peroxidase stock solution (200 U/mL), 50 μL of the cholesterol oxidase stock solution (200 U/mL), and 5 μL cholesterol esterase stock solution (200 U/mL) to 4.82 mL of 1X Reaction Buffer. The fluorescence was measured using a plate reader at an excitation of 560 nm and an emission of 590 nm. RFUs were converted to cholesterol concentration using a standard curve for cholesterol reference standard. Serum samples were assayed for HDL and LDL/VLDL according to the manufacturer's protocols using the HDL and LDL/VLDL assay kit (Abcam, Catalog number ab65390). Briefly, the HDL and LDL/VLDL components were separated using the precipitation buffer provided with the kit. These separated components or cholesterol standards (50 μL in volume) were incubated with 50 μL of fluorimetric reaction mixture, comprising of cholesterol assay buffer (45.6 μL), cholesterol probe (0.4 μL), enzyme mix (2 μL), and cholesterol esterase (2 μL) for 1 h at 37 ºC in a 96 well plate. Fluorescence was measured with an excitation wavelength of 538 nm and an emission wavelength of 587 nm. The standard curve generated was used to quantify the HDL or LDL/VDL present in the samples. Cytokines TNF-α, IL-6, IL-1β, and MCP-1 in the serum from saline or NP treated animals were quantified by ELISA using kits obtained from BD Biosciences. The 96-well plates were first coated with capture antibody for overnight incubation at 4 °C and then blocked using assay diluent (10% FBS in PBS) for 1 h at room temperature. The wells were then aspirated and washed 3 times with 0.05% Tween20 in PBS (~300 μL each wash). Then, either serum samples diluted with assay diluent or standard solutions (100 μL) were added into the wells and incubated for 2 h at room temperature. The wells were then aspirated and washed 5 times with wash buffer (~300 μL each wash). The detection antibody was then added and incubated for 1

h at room temperature, followed by washing with wash buffer (5 times) and 20 min incubation of enzyme reagent (SAv-HRP) at room temperature. Then the wells were washed 7 times with the wash buffer and the substrate solution was added into each well and incubated for 15 min at room temperature in the dark. Finally, the absorbance was measured at 450 nm within 30 min after stopping the reaction with 2 M H_2SO_4.

Therapeutic Study in ApoE$^{-/-}$ Mice Fed With Normal Chow Diet. ApoE$^{-/-}$ mice of age five weeks were purchased from Jackson Laboratory, Bar Harbor, ME. These animals were fed on normal chow diet. All the animals had free access to food and water at all times during the whole experiment. Saline, T-CO_{40}-HDL-NPs, or NT-CO_{40}-HDL-NPs (10 mg/kg/injection with respect to total NP) were injected intravenously *via* tail vein twice weekly. Blood samples (50 μL) were collected prior to injection and after treatment. These blood samples were then centrifuged at 1500xg for 20 min at 4 °C in order to isolate serum. The serum samples were analyzed for cholesterol, triglyceride and HDL/LDL levels following similar protocol as described for the BALB/c mice. ELISA was also performed on the serum samples to determine the levels of cytokines (IL-6, TNF-α and IL-10) following similar protocol as described previously for BALB/c albino mice. Organ sample sections were fixed in 10% neutral-buffered formalin, routinely processed, embedded in paraffin, sectioned approximately 5 μm, mounted on glass slides, and stained with hematoxylin and eosin for histological analysis. For heart samples, orange paraffin blocks each with one transverse section of heart were used. 4 μm sections were made and stained with hematoxylin and eosin. Myocardial necrosis and lipid accumulation were scored. Oil Red O was used to stain the lipid in aorta. The formalin-fixed aortas were dissected away from the fat and transected from the heart at the aortic

valve. The aortas were opened longitudinally and placed in Oil Red O (80% solution of commercial product) for 20 mins, and then rinsed in water. The intimal surface was photographed under a dissecting microscope.

Table S1. Characterization of T-HDL-NP library from three independent experiments					
	$Z_{Average}$ (nm)	Zeta Potential (mV)	Polydispersity index (PDI)	%CO Loading	%EE of CO
T-CO_{10}-HDL-NP	222.0±41.5	49.9±8.3	0.16±0.03	5.2±0.1	49.4±1.2
T-CO_{20}-HDL-NP	166.4±0.4	49.7±9.6	0.19±0.09	9.4±2.2	41.8±10.6
T-CO_{30}-HDL-NP	157.6±2.3	55.5±10.6	0.15±0.07	12.7±2.9	34.2±8.7
T-CO_{40}-HDL-NP	151.6±0.8	51.2±6.9	0.12±0.04	17.4±4.5	31.9±9.7
T-CO_{50}-HDL-NP	145.4±0.7	55.2±3.6	0.15±0.02	22.3±4.7	29.0±7.5
T-CO_{60}-HDL-NP	143.4±2.7	53.1±8.5	0.14±0.02	27.0±5.1	24.9±6.2
T-CO_{70}-HDL-NP	138.6±4.0	49.9±6.6	0.11±0.01	34.2±5.6	22.6±5.4
T-CO_{80}-HDL-NP	131.3±5.5	45.3±14.5	0.13±0.01	45.0±5.9	20.8±4.7
T-CO_{90}-HDL-NP	166.0±22.9	46.5±12.9	0.15±0.02	69.8±4.0	26.0±4.6

Table S2. Characterization of NT-HDL-NP library from three independent experiments

	$Z_{Average}$ (nm)	Zeta Potential (mV)	Polydispersity index (PDI)	%CO Loading	%EE of CO
NT-CO_{10}-HDL-NP	129.3±15.1	-32.4±2.4	0.17±0.05	1.5±0.1	13±0.8
NT-CO_{20}-HDL-NP	132.8±19.5	-29.9±8.3	0.17±0.07	2.8±0.2	11.3±0.7
NT-CO_{30}-HDL-NP	138.1±23.8	-31.6±6.9	0.19±0.08	6.3±0.5	14.7±1.2
NT-CO_{40}-HDL-NP	129.1±6.9	-35.2±5.7	0.18±0.04	7.9±0.4	12±0.6
NT-CO_{50}-HDL-NP	140.9±11.7	-32.9±7.6	0.22±0.11	9.9±0.2	9.9±0.2
NT-CO_{60}-HDL-NP	123.9±18.6	-33.8±5.5	0.19±0.03	15.2±0.7	10.1±0.5
NT-CO_{70}-HDL-NP	123.5±25.4	-33.1±4.8	0.22±0.06	18.6±0.5	7.9±0.2
NT-CO_{80}-HDL-NP	128.5±19.3	-30.2±4.9	0.21±0.06	24.8±0.3	6.2±0.1
NT-CO_{90}-HDL-NP	133.9±12.3	-28.6±6.9	0.22±0.05	47.3±0.7	5.3±0.1

Table S3. Characterization of NPs used in distribution studies in BALB/c mice			
	Hydrodynamic diameter (nm)	Zeta potential (mV)	PDI
T-CO_{40}-QD-HDL-NPs	161.4± 0.7	31.4±0.6	0.133±0.015
T-CO_{70}-QD-HDL-NPs	156.1±3.1	37.2±0.7	0.261±0.004
NT-CO_{40}-QD-HDL-NPs	173.8±1.0	-31.8±0.6	0.157±0.019
NT-CO_{70}-QD-HDL-NPs	165.0±5.2	-30.5±0.2	0.197±0.015

Table S4. Characterization of T-CO_{40}-HDL-NPs and NT-CO_{40}-HDL-NPs used in studies with $ApoE^{(-/-)}$ mice fed with normal Chow diet.

Injection Number	Sample Name	Diameter (nm) ($Z_{average}$)	PDI	ZP (mV)	CO loading %L (%EE)
1	T-CO_{40}-HDL-NPs	146.9±0.7	0.112	29.8±1.9	2.7 (4.2)
1	NT-CO_{40}-HDL-NPs	130.1±3.3	0.162	-25.4±1.3	2.6 (4.0)
2	T-CO_{40}-HDL- NPs	178.7±1.2	0.144	20.6±.7	5.9 (9.4)
2	NT-CO_{40}-HDL- NPs	160.60±.7	0.123	-33.0±2.2	6.3 (10.1)
3	T-CO_{40}-HDL-NPs	177.5±2.8	0.119	16.8±1.8	7.6 (12.2)
3	NT-CO_{40}-HDL-NPs	179.0±14.1	0.141	-30.0±0.7	9.0 (14.9)
4	T-CO_{40}-HDL-NPs	175.5±1.1	0.087	30.3±2.9	7.6 (12.4)
4	NT-CO_{40}-HDL-NPs	177.7±1.3	0.130	-34.9±2.2	9.3 (15.4)
5	T-CO_{40}-HDL-NPs	173.1±2.3	0.110	21.7±1.2	6.6 (10.5)
5	NT-CO_{40}-HDL-NPs	186.4±2.9	0.175	-28.0±.2	9.1 (15.0)
6	T-CO_{40}-HDL-NPs	158.1±1.4	0.111	27.1±2.1	5.6 (8.9)
6	NT-CO_{40}-HDL-NPs	189.4±3.4	0.180	-27.1±.5	10.2 (17.0)
7	T-CO_{40}-HDL-NPs	164.6±1.4	0.093	41.2±1.7	20.8 (39.7)
7	NT-CO_{40}-HDL-NPs	186.4±3.0	0.175	-28.0±0.2	15.1 (26.6)

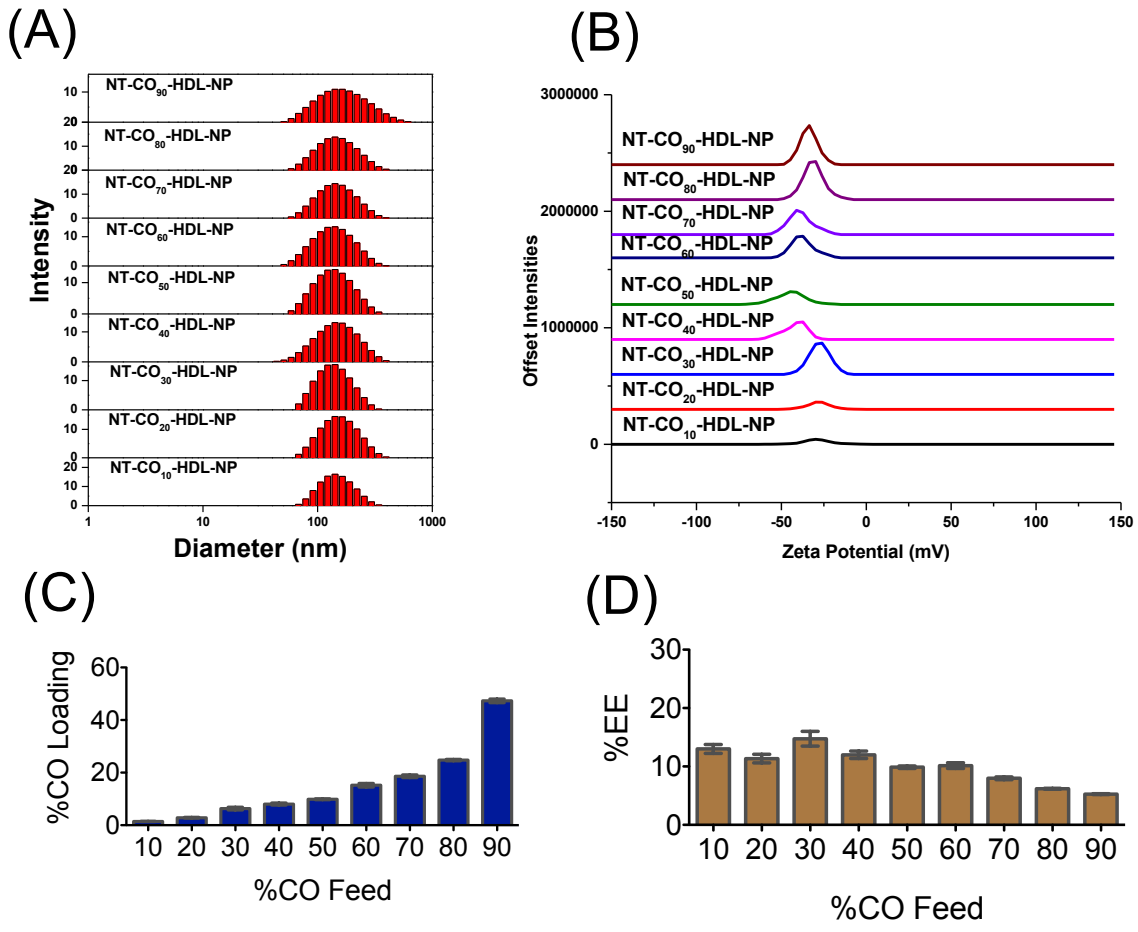

Fig. S1. Overlay of DLS plots of (A) diameter, (B) zeta potential, (C) percent loading of CO, and (D) percent encapsulation efficiency (EE) of CO in NT-HDL-NPs.

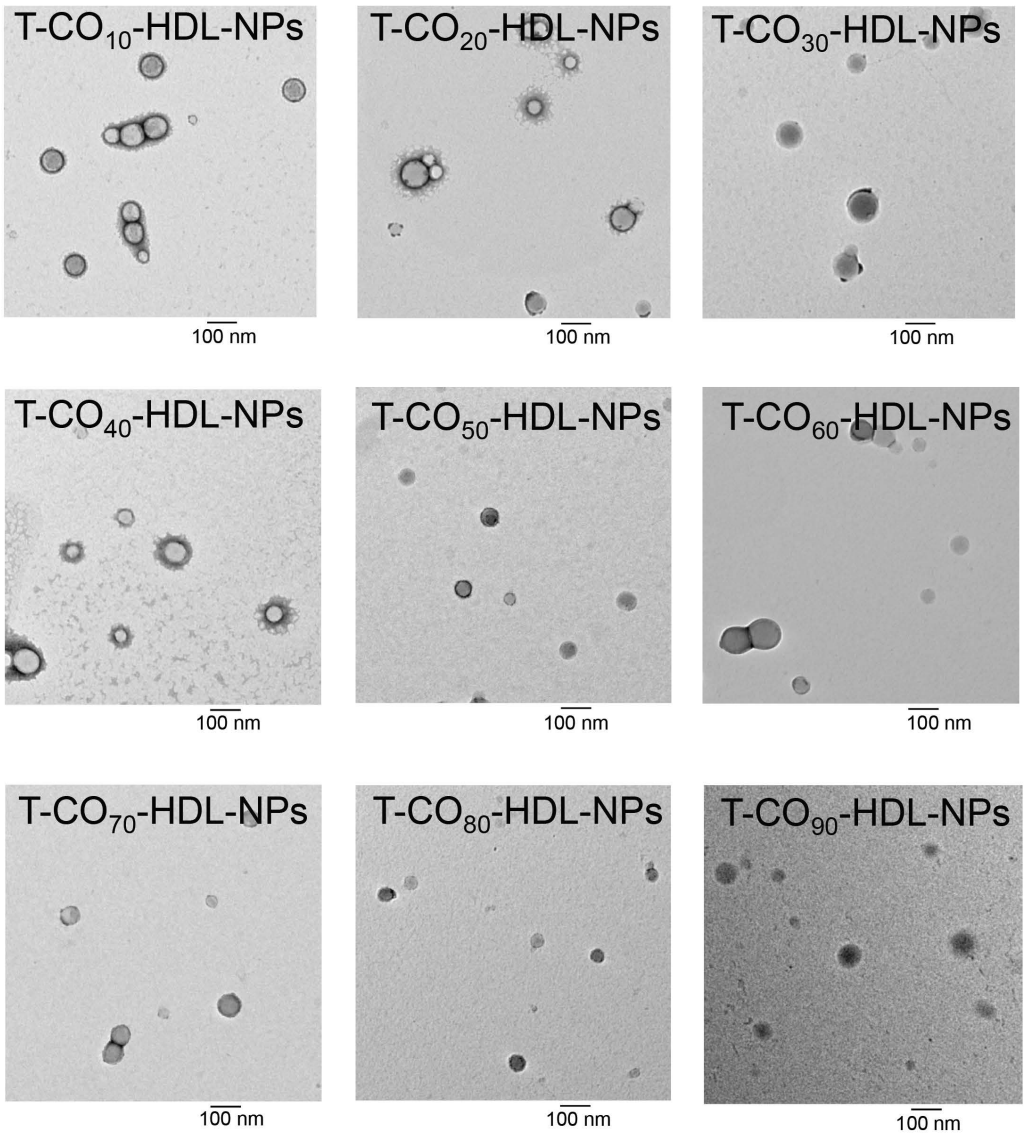

Fig. S2. TEM images of library of T-HDL-NPs.

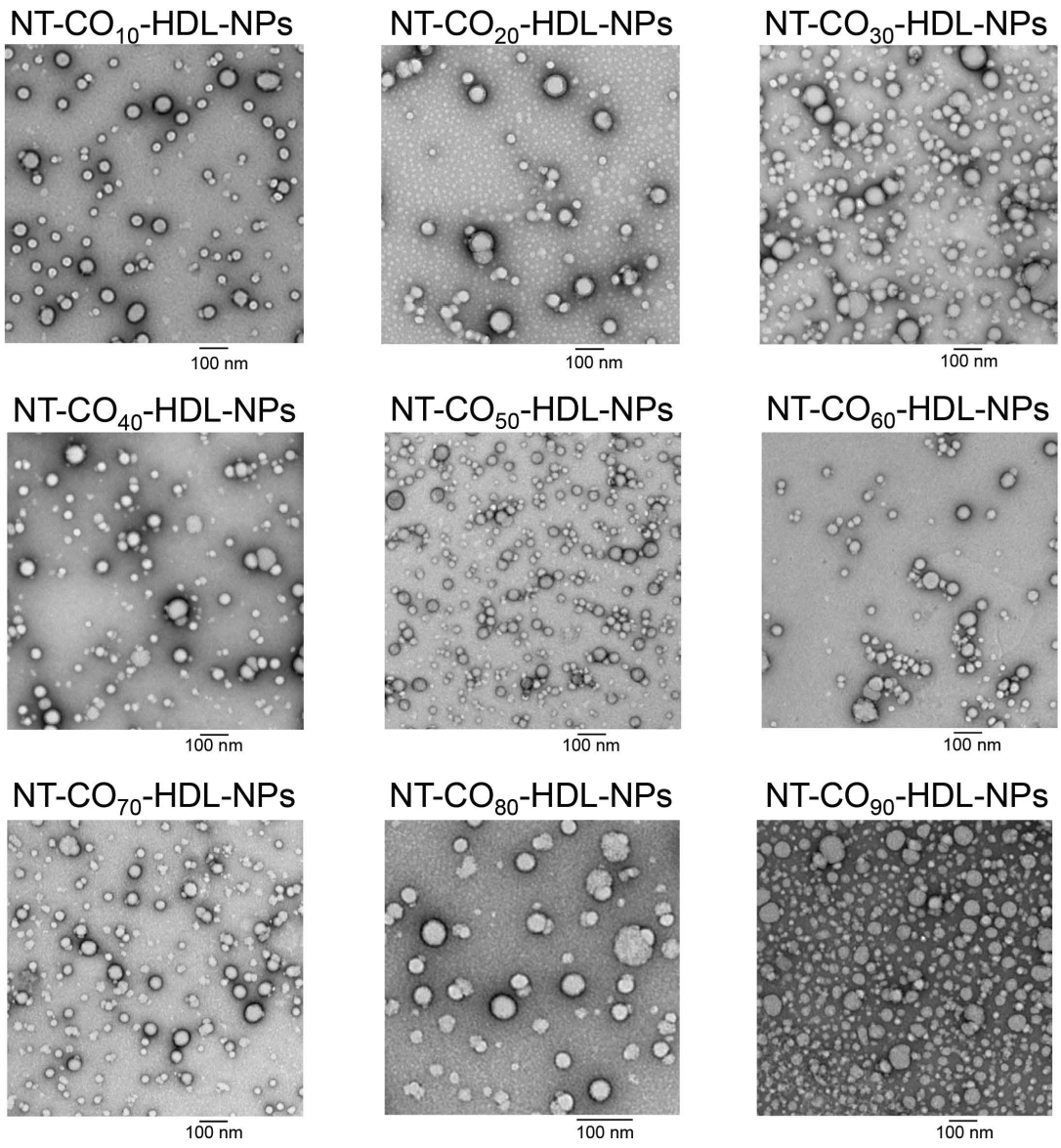

Fig. S3. TEM images of library of NT-HDL-NPs.

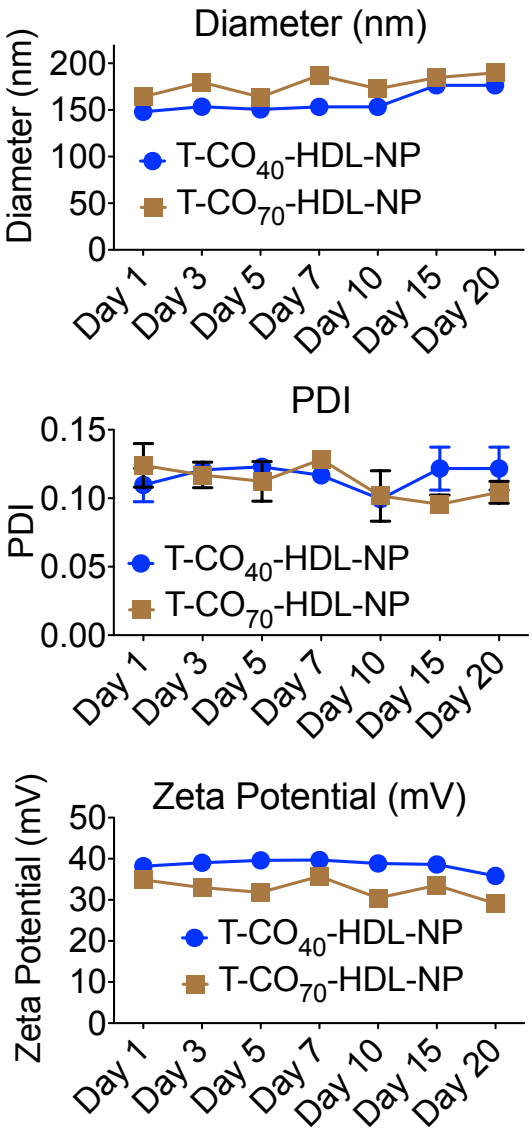

Fig. S4. Stability of HDL-mimicking NPs (0.5 mg/mL) in water at 37 °C as determined by comparing size, polydispersity, and zeta potential up to 3 weeks.

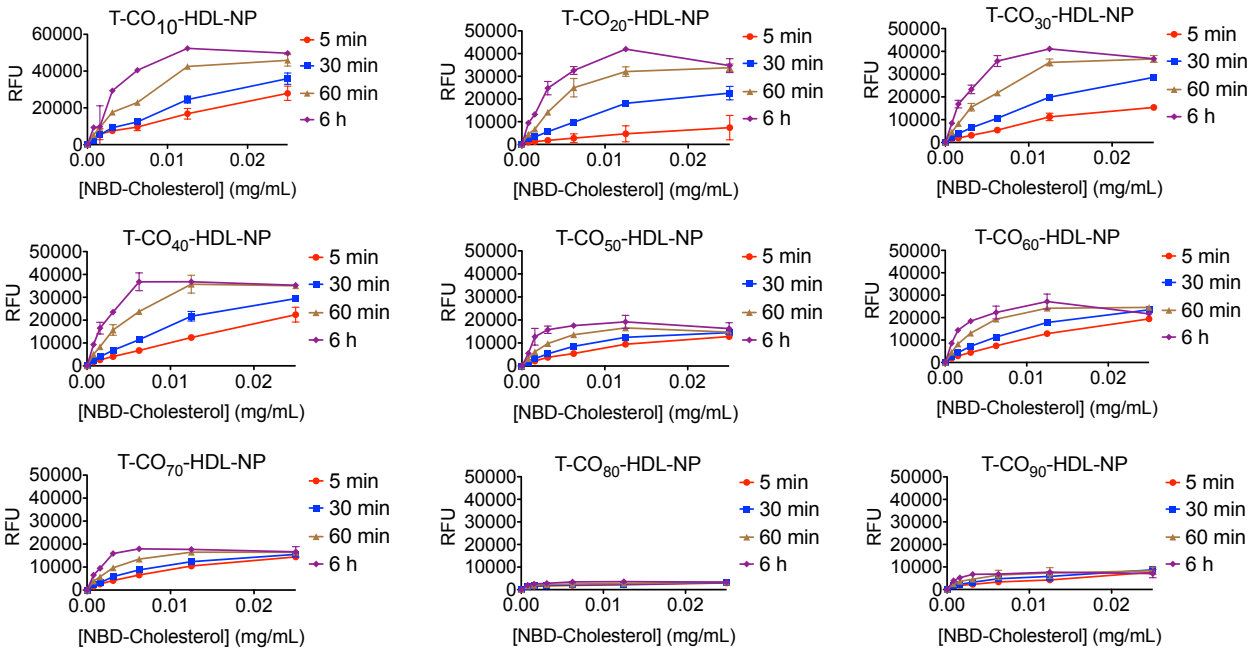

Fig. S5. Comparison of time dependent NBD-cholesterol binding profiles of the T-HDL-NP (0.025 mg/mL) library with varied %CO feed. RFU: Relative fluorescence unit.

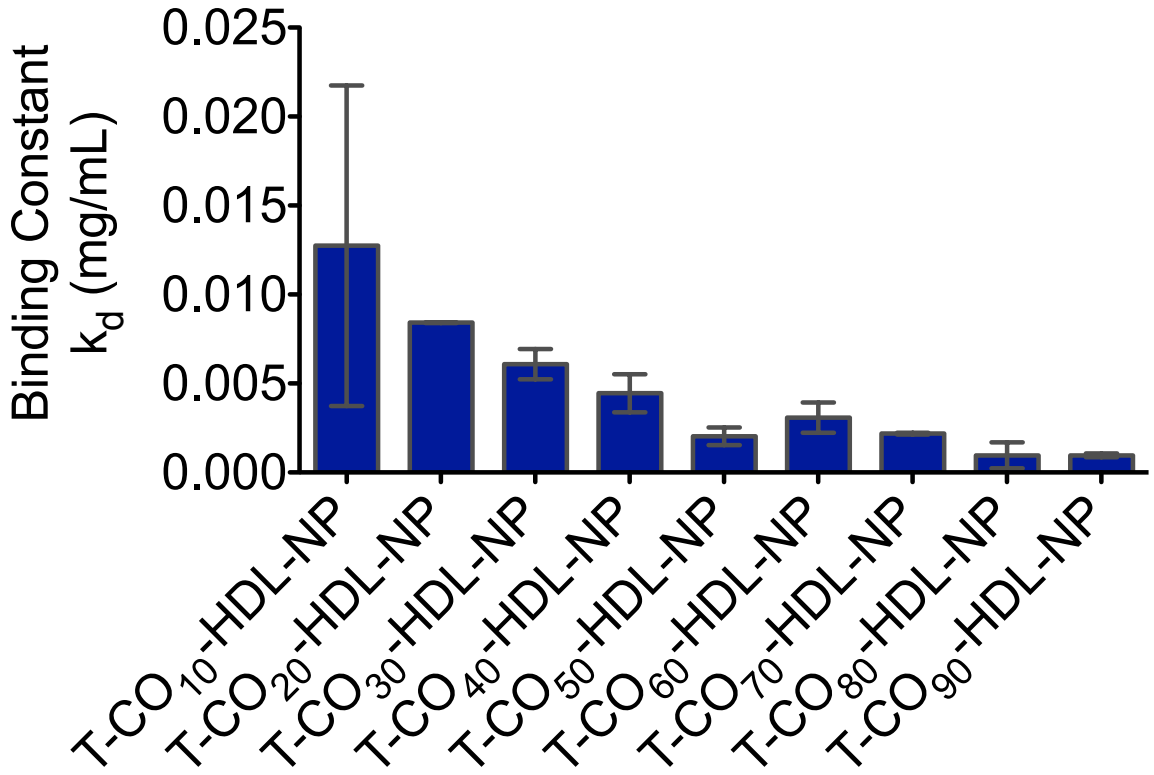

Fig. S6. Comparison of NBD-cholesterol binding constants at 6 h of T-HDL-NP library.

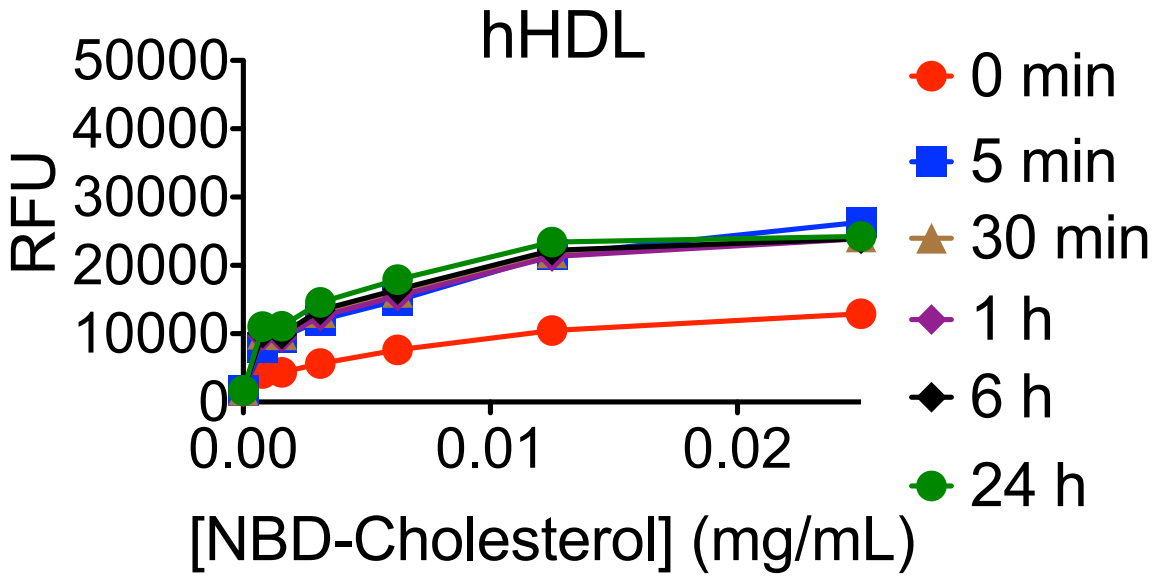

Fig. S7. Time dependent NBD-cholesterol binding profiles of hHDL (0.025 mg/mL). RFU: Relative fluorescence unit.

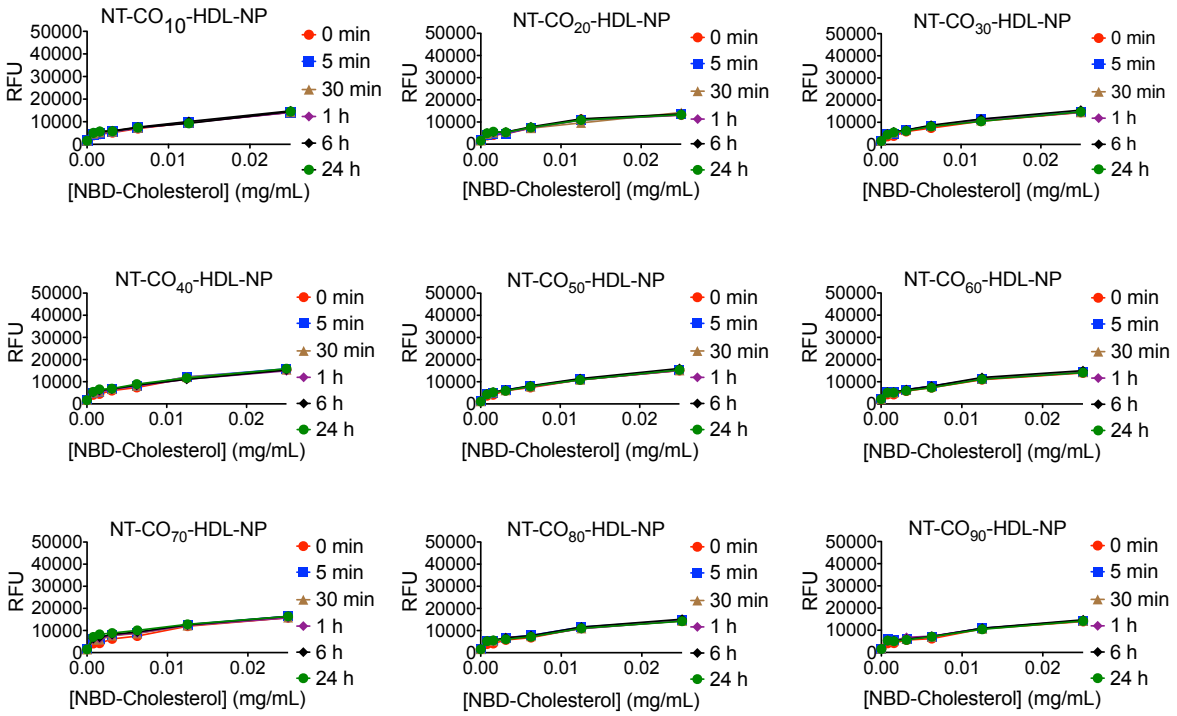

Fig. S8. Comparison of time dependent NBD-cholesterol binding profiles of the NT-HDL-NP (0.025 mg/mL) library with varied various %CO feed. RFU: Relative fluorescence unit.

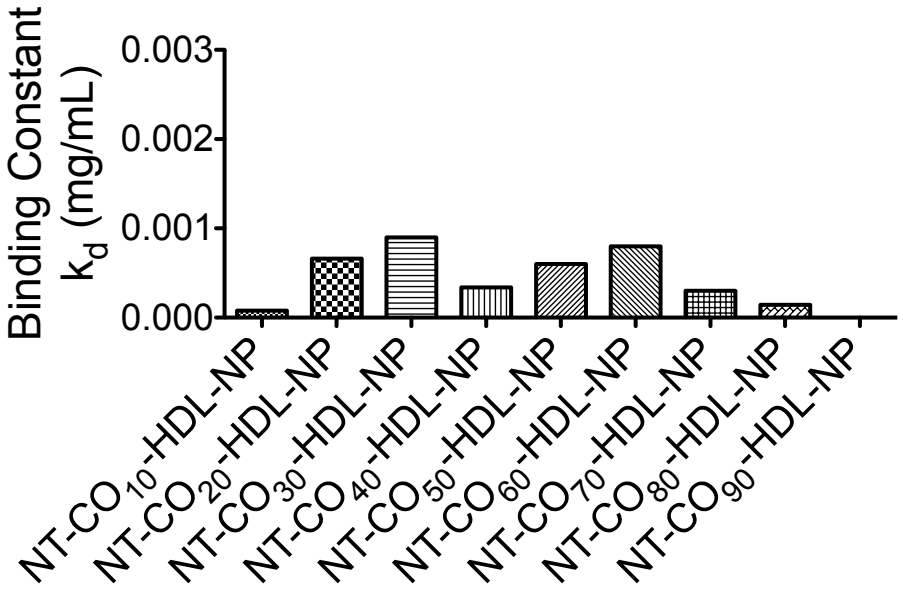

Fig. S9. Comparison of NBD-cholesterol binding constants at 6 h of the NT-HDL-NP library.

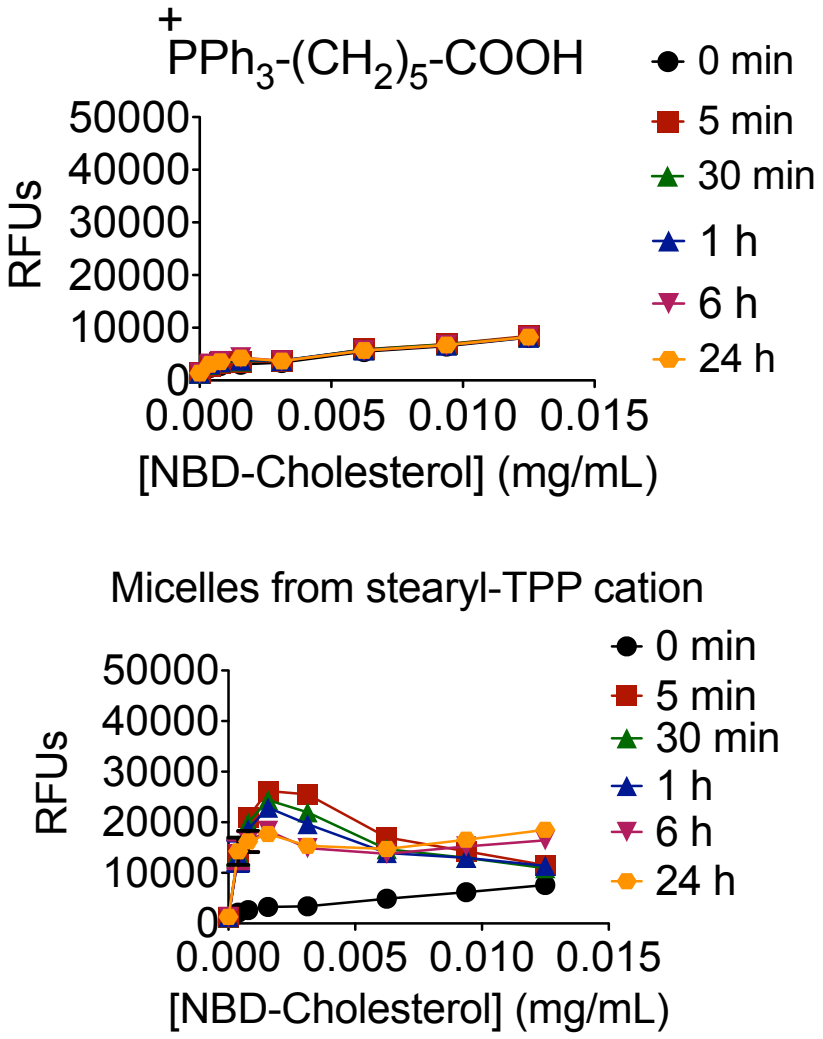

Fig. S10. Time dependent NBD-cholesterol binding profiles of TPP-$(CH_2)_5$-COOH (0.012 mg/mL) and micelles (0.012 mg/mL) constructed with stearyl-TPP. RFU: Relative fluorescence unit.

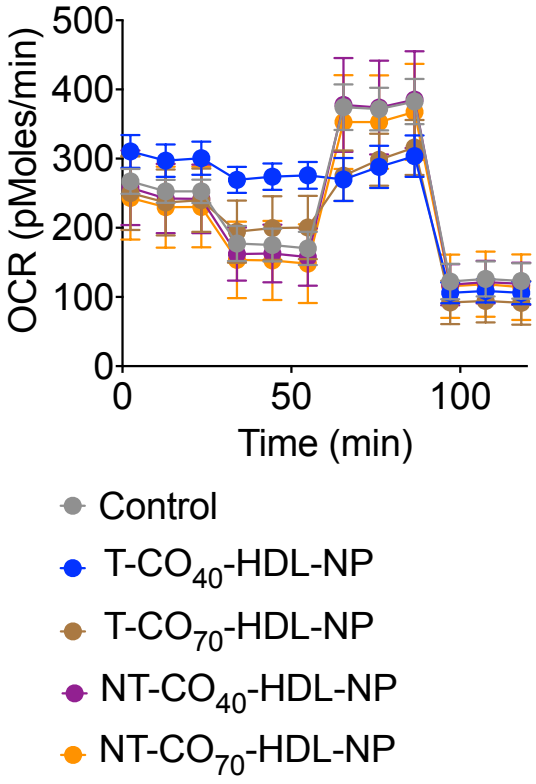

Fig. S11. MitoStress assay on H9C2 cardiomyocytes in presence of HDL mimicking NPs. The cells were treated with T/NT-C_{40}-HDL-NP (50 μg/mL with respect to total NP) and T/NT-C_{70}-HDL-NP (50 μg/mL with respect to total NP) for 4 h at 37 °C under 5% CO_2 atmosphere and mitostress assay was performed. Electron transport inhibitor oligomycin, 2.0 μM; ionophore FCCP, 2.0 μM; a mixture of antimycin-A complex III inhibitor, 1.0 μM and rotenone, a complex I inhibitor 1.0 μM were used. Test articles on each well had four replicates.

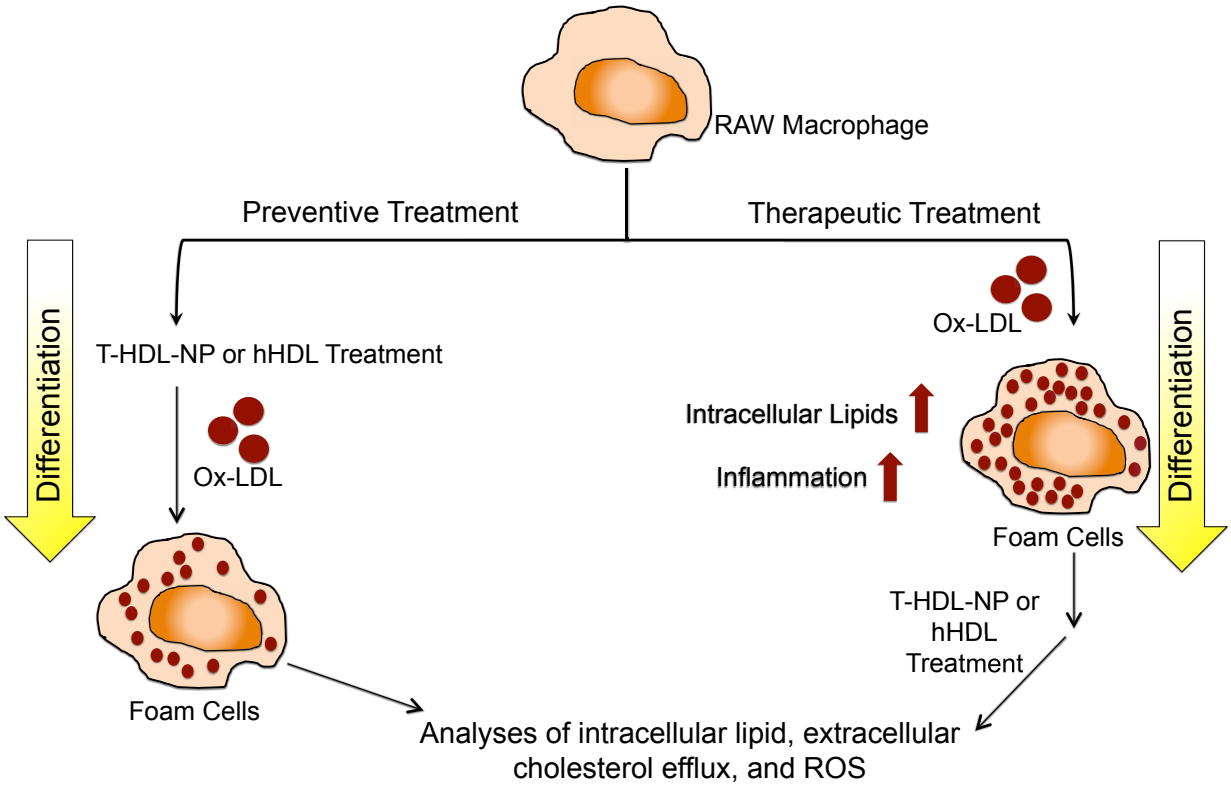

Fig. S12. Experimental design to study RCT mimicking properties of T-CO_{40}-HDL-NPs and T-CO_{70}-HDL-NPs using macrophage derived foam cells under preventive and therapeutic settings.

References:

1. Marrache, S.; Dhar, S., Biodegradable synthetic high-density lipoprotein nanoparticles for atherosclerosis. *Proc Natl Acad Sci USA* **2013,** *110* (23), 9445-9450.