

Analyzing 2,000 *in vivo* Drug Delivery Data Points Reveals Cholesterol Structure Impacts Nanoparticle Delivery

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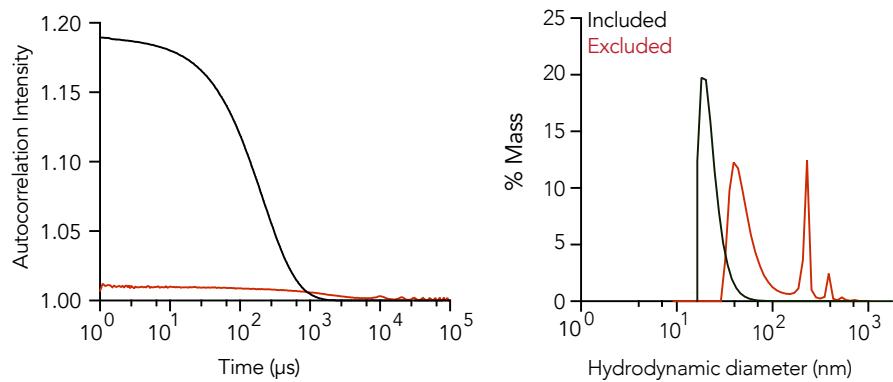
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Supplementary Figure 1. **(A)** A library of 141 LNPs was formulated to test 6 cholesterol variants using 8 different molar ratios. **(B)** LNPs were pooled based on whether or not they met our inclusion criteria: autocorrelation curves with 1 inflection point and hydrodynamic diameters between 20 nm and 200 nm, based on dynamic light scattering (DLS). Representative FACs gates for sorting of lung **(C)** and spleen **(D)** endothelial cells and macrophages, as well as liver **(E)** endothelial cells and hepatocytes. **(F)** Data normalization after sequencing of individual cell types yields relative distribution of different LNPs to cell types and tissues. **(G)** More than 50% of LNPs of every cholesterol type met our inclusion criteria and were pooled and analyzed. **(H)** Diameter distributions for all LNPs, subdivided by cholesterol type. **(I)** Diameter plotted against distribution across all WT cell types in all tissues. **(J)-(P)** LNP diameter, subdivided by cholesterol variant, plotted against whole animal distribution for WT, VLDLR^{-/-}, and LDLR^{-/-} mice, with corresponding R² values shown in **(Q)**.

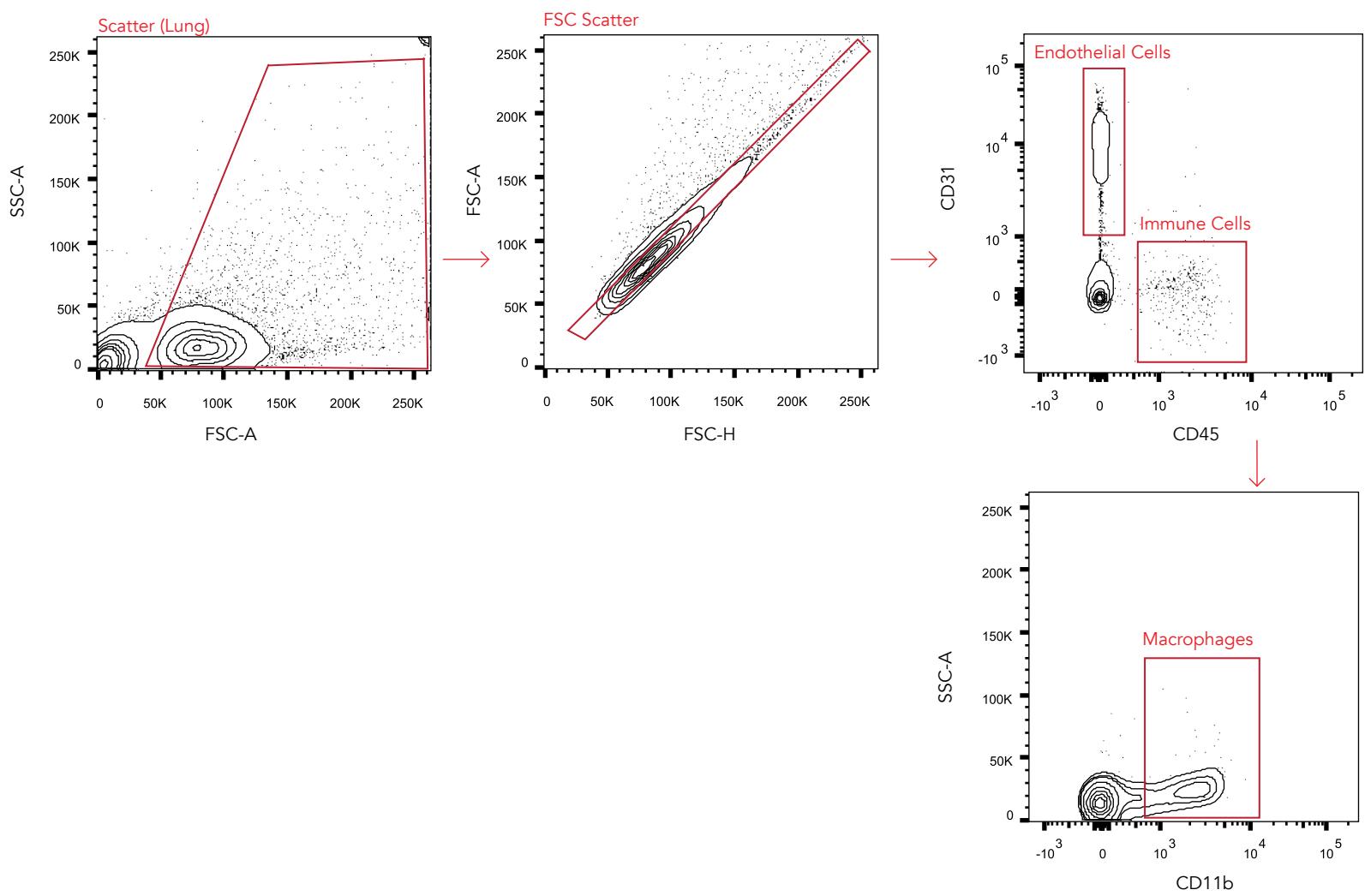
A

LNP #	Lipomer	Cholesterol	PEG MW	PEG Chain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %
1	7C1	4B-OH Cholesterol	2000	C14	-	62	30	8	0
2	7C1	4B-OH Cholesterol	2000	C14	-	35	60	5	0
3	7C1	4B-OH Cholesterol	2000	C14	-	62	22	16	0
4	7C1	4B-OH Cholesterol	2000	C14	-	35	35	30	0
5	7C1	No Cholesterol	2000	C14	-	80	0	20	0
6	7C1	4B-OH Cholesterol	2000	C14	-	80	15	5	0
7	7C1	4B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	50	40	2
8	7C1	4B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	29	29	11
9	7C1	4B-OH Cholesterol	2000	C14	18:1 LysO PC	50	29	11	10
10	7C1	4B-OH Cholesterol	2000	C14	18:1 LysO PC	50	40	2	8
11	7C1	4B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8
12	7C1	4B-OH Cholesterol	2000	C14	Biotinyl PE	50	29	11	10
13	7C1	4B-OH Cholesterol	2000	C14	DC Chol-HCl	50	29	11	10
14	7C1	4B-OH Cholesterol	2000	C14	DC Chol-HCl	50	40	2	8
15	7C1	4B-OH Cholesterol	2000	C14	DMPC	50	29	11	10
16	7C1	4B-OH Cholesterol	2000	C14	DMPC	50	40	2	8
17	7C1	4B-OH Cholesterol	2000	C14	DOPC	50	29	11	10
18	7C1	4B-OH Cholesterol	2000	C14	DOPC	50	40	3	8
19	7C1	4B-OH Cholesterol	2000	C14	DOPC	50	40	2	8
20	7C1	4B-OH Cholesterol	2000	C14	DOPC	50	29	11	10
21	7C1	4B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10
22	7C1	4B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8
23	7C1	4B-OH Cholesterol	2000	C14	O Chems PC	50	29	11	10
24	7C1	4B-OH Cholesterol	2000	C14	O Chems PC	50	40	2	8
25	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0
26	7C1	7A-OH Cholesterol	2000	C14	-	80	15	5	0
27	7C1	No Cholesterol	2000	C14	-	80	0	20	0
28	7C1	7A-OH Cholesterol	2000	C14	-	35	60	5	0
29	7C1	7A-OH Cholesterol	2000	C14	-	62	22	16	0
30	7C1	7A-OH Cholesterol	2000	C14	-	35	35	30	0
31	7C1	7A-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	29	11	10
32	7C1	7A-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	40	2	8
33	7C1	7A-OH Cholesterol	2000	C14	18:1 LysO PC	50	29	11	10
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35	7C1	7A-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8
36	7C1	7A-OH Cholesterol	2000	C14	DC Chol-HCl	50	29	11	10
37	7C1	7A-OH Cholesterol	2000	C14	DC Chol-HCl	50	40	2	8
38	7C1	7A-OH Cholesterol	2000	C14	DMPC	50	40	2	8
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42	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	29	11	10
43	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8
44	7C1	7A-OH Cholesterol	2000	C14	DOTAP	50	29	11	10
45	7C1	7A-OH Cholesterol	2000	C14	O Chems PC	50	29	11	10
46	7C1	7B-OH Cholesterol	2000	C14	-	80	15	5	0
47	7C1	No Cholesterol	2000	C14	-	80	0	20	0
48	7C1	7B-OH Cholesterol	2000	C14	-	62	30	8	0
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54	7C1	7B-OH Cholesterol	2000	C14	18:1 LysO PC	50	40	2	8
55	7C1	7B-OH Cholesterol	2000	C14	18:1 LysO PC	50	29	11	10
56	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	29	11	10
57	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8
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80	7C1	Cholesterol	2000	C14	18:1 LysO PC	50	40	2	8
81	7C1	Cholesterol	2000	C14	18:1 LysO PC	50	29	11	10
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88	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8
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92	7C1	Cholesterol	2000	C14	DOTAP	50	29	11	10
93	7C1	Cholesterol	2000	C14	DOTAP	50	40	2	8
94	7C1	Cholesterol	2000	C14	DSPC	50	29	11	10
95	7C1	Cholesterol	2000	C14	DSPC	50	40	2	8
96	7C1	Cholesterol	2000	C14	O Chems PC	50	40	2	8
97	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10
98	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0
99	7C1	No Cholesterol	2000	C14	-	80	0	20	0
100	7C1	Cholesteryl Oleate	2000	C14	-	35	60	5	0
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106	7C1	Cholesteryl Oleate	2000	C14	18:1 LysO PC	50	29	11	10
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118	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10
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123	7C1	Cholesteryl Oleate	2000	C14	O Chems PC	50	29	11	10
124	7C1	No Cholesterol	2000	C14	-	62	22	16	0
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126	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0
127	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0
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130	7C1	Cholesteryl Stearate	2000	C14	16:0 - 18:1 PC	50	40	2	8
131	7C1	Cholesteryl Stearate	2000	C14	18:1 LysO PC	50	29	11	10
132	7C1	Cholesteryl Stearate	2000	C14	DC Chol-HCl	50	40	2	8
133	7C1	Cholesteryl Stearate	2000	C14	DC Chol-HCl	50	29	11	10
134	7C1	Cholesteryl Stearate	2000	C14	DMPC	50	40	2	8
135	7C1	Cholesteryl Stearate	2000	C14	DOPC	50	29	11	10
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137	7C1	Cholesteryl Stearate	2000	C14	DOTAP	50	2		

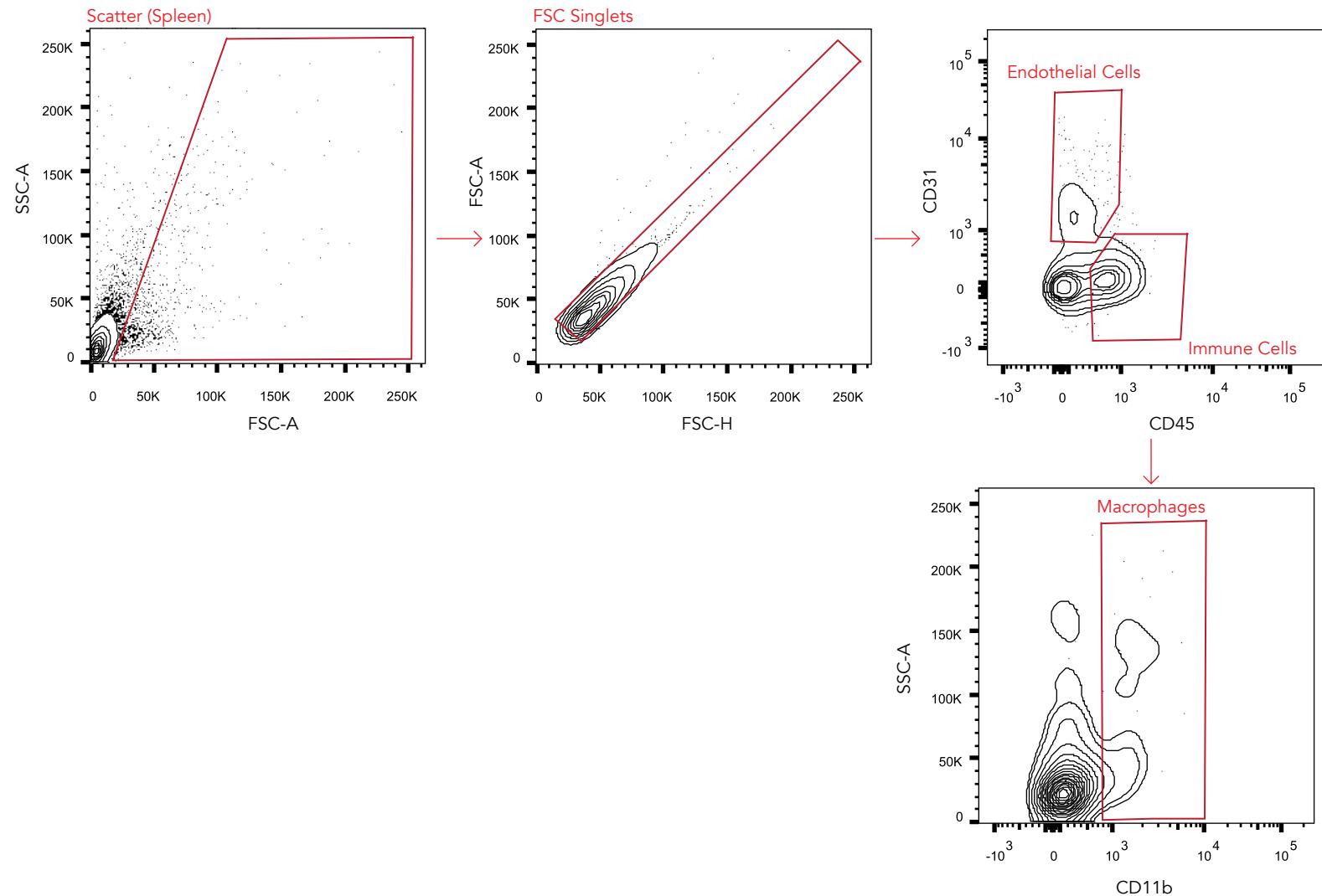
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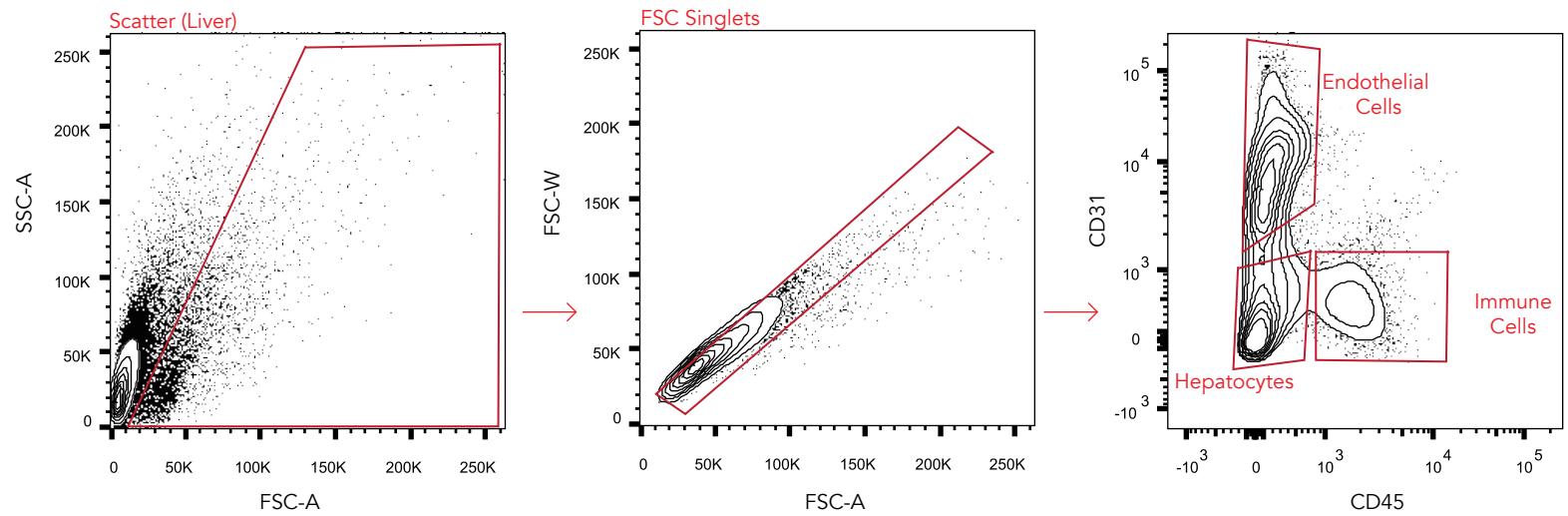
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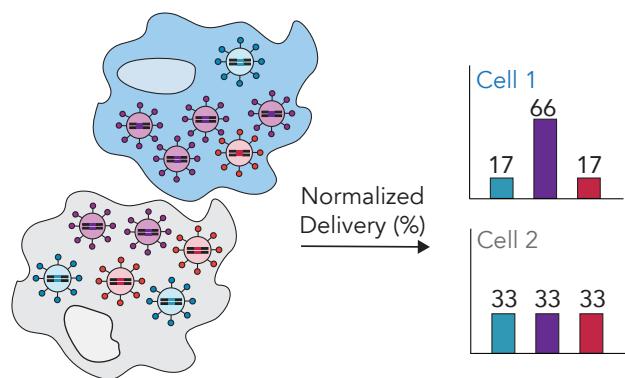
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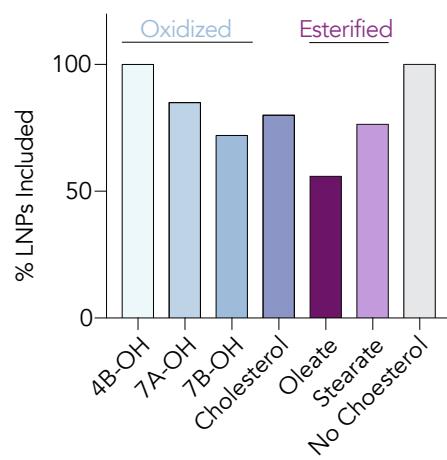
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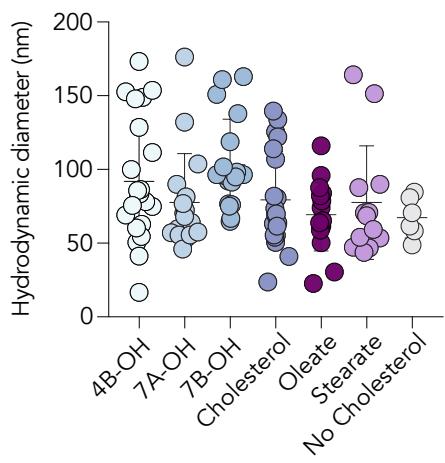
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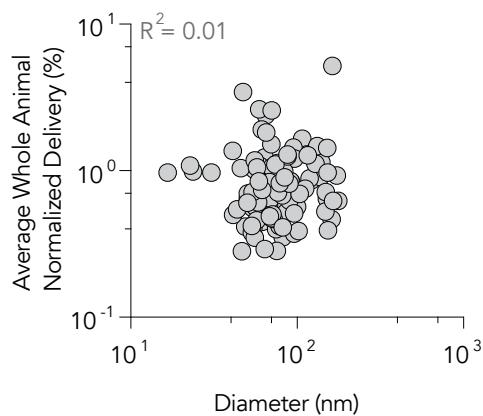
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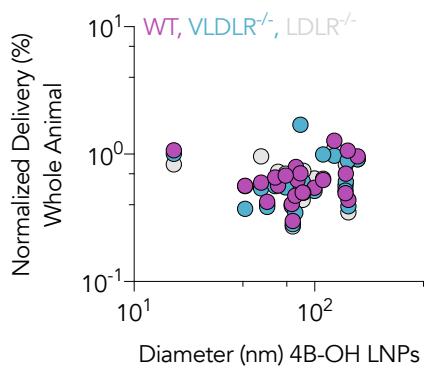
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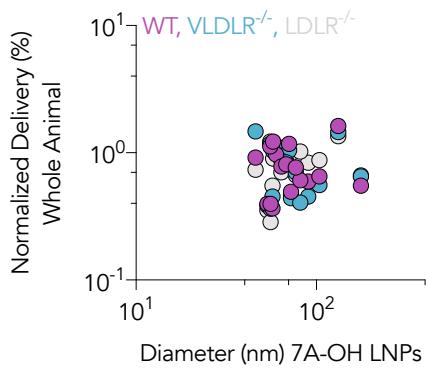
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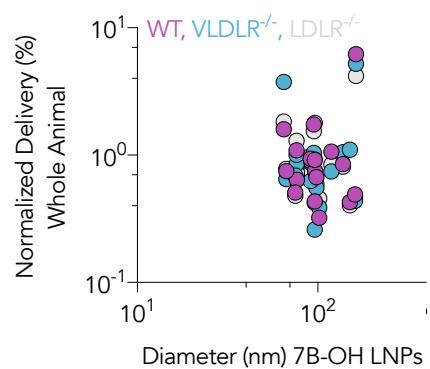
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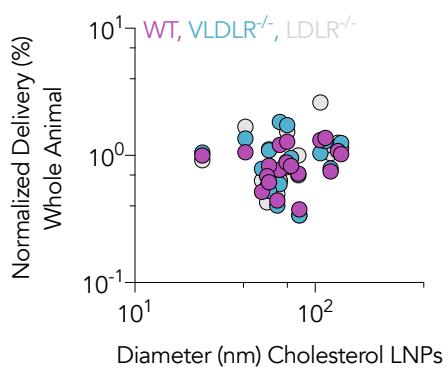
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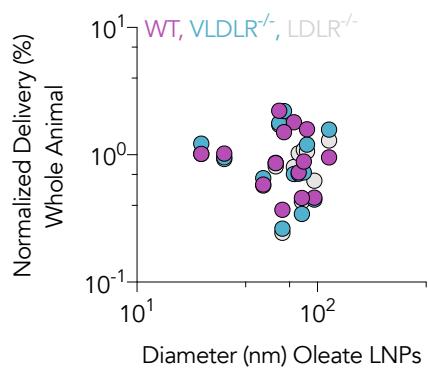
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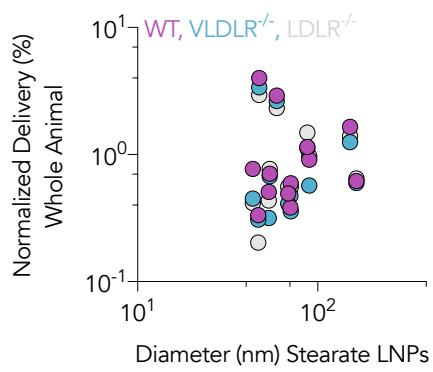
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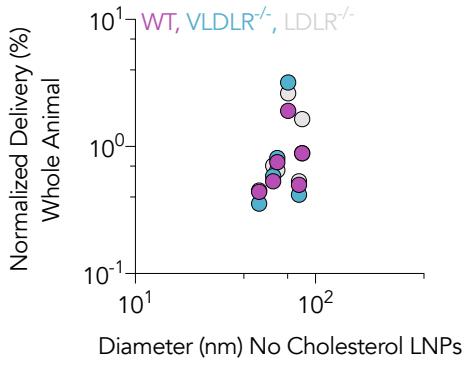
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O



P



Q

	Size vs. WT	Size vs. VLDLR ^{-/-}	Size vs. LDLR ^{-/-}
4B-OH	.052	.023	.043
7A-OH	.001	.001	.046
7B-OH	.144	.058	.058
Cholesterol	.094	.017	.112
Oleate	.006	.002	.002
Stearate	.010	.010	.0003
No Cholesterol	.071	.034	.171

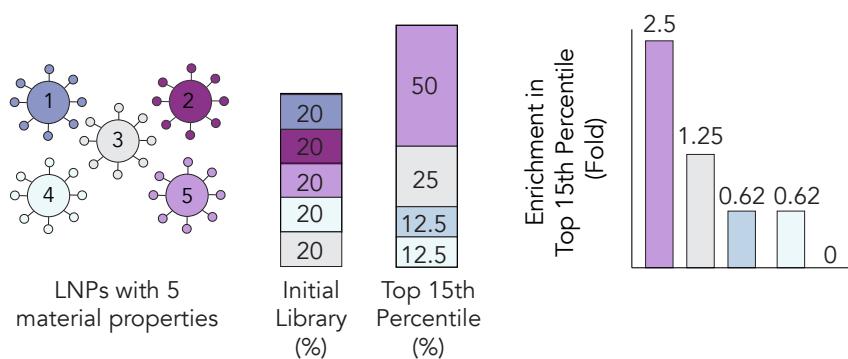
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R^2

Supplementary Figure 2. Cholesterol structure can alter nanoparticle delivery *in vivo*.

(A) Schematic (not real data; cartoon data simplified for this example) showing enrichment for 5 LNP properties; initially, each LNP property is represented 20% of the time in all LNPs. However, property 5 is represented 50% of the time in the top 15% of LNPs. We would consider this a 2.5-fold enrichment in the top 15%. Composition and formulation ratios of the top 15% of LNPs in each cell type in **(B)** WT, **(C)** VLDLR^{-/-}, and **(D)** LDLR^{-/-} mice. **(E-J)** LNP diameter plotted against delivery in top performing LNPs in each cell type in WT, LDLR^{-/-}, and VLDLR^{-/-} mice, with corresponding R² values shown in **(K)**. Normalized delivery for all LNPs in **(L,M)** LDLR^{-/-} and **(N,O)** VLDLR^{-/-} mice, subdivided by cholesterol type. Enrichment in the top 15% of LNPs in **(P,Q)** LDLR^{-/-} and **(R,S)** VLDLR^{-/-} mice, subdivided by cholesterol type.

A

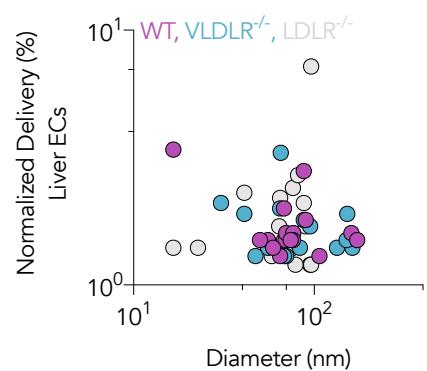


Lung Endothelial Cells										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	5.7
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	4.7
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	4.1
81	7C1	7A-OH Cholesterol	2000	C14	DMPC	50	29	11	10	3.9
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	3.3
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	2.4
137	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0	2.4
56	7C1	4B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	40	2	8	2.2
77	7C1	7A-OH Cholesterol	2000	C14	18:1 Lyso PC	50	29	11	10	2.1
123	7C1	Cholesteryl Oleate	2000	C14	DOPC	50	40	2	8	2.1
128	7C1	Cholesteryl Oleate	2000	C14	DC Chol-HCl	50	29	11	10	1.8
130	7C1	Cholesteryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	1.8
129	7C1	Cholesteryl Oleate	2000	C14	DC Chol-HCl	50	40	2	8	1.5
27	7C1	7B-OH Cholesterol	2000	C14	18:1 Lyso PC	50	29	11	10	1.5
113	7C1	No Cholesterol	2000	C14	-	80	0	20	0	1.5
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.5
Lung Macrophages										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	16.8
120	7C1	Cholesteryl Oleate	2000	C14	DMPC	50	29	11	10	7.4
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	5.1
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	3.4
124	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10	2.7
137	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0	2.5
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	2.5
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	2.4
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	2.3
104	7C1	Cholesteryl Stearate	2000	C14	DOTAP	50	29	11	10	2.0
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	1.7
114	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0	1.6
97	7C1	7A-OH Cholesterol	2000	C14	-	35	60	5	0	1.5
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	1.4
125	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	40	2	8	1.4
14	7C1	Cholesterol	2000	C14	DC Chol-HCl	50	40	2	8	1.3
Splenic Endothelial Cells										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
109	7C1	Cholesteryl Stearate	2000	C14	DSPC	50	40	2	8	6.0
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	5.0
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	3.5
6	7C1	Cholesterol	2000	C14	DMPC	50	40	2	8	2.6
125	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	40	2	8	2.5
56	7C1	4B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	40	2	8	2.4
40	7C1	7B-OH Cholesterol	2000	C14	DC Chol-HCl	50	40	2	8	2.4
70	7C1	4B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	2.1
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	2.0
9	7C1	Cholesterol	2000	C14	DOTAP	50	29	11	10	2.0
95	7C1	7A-OH Cholesterol	2000	C14	-	80	15	5	0	1.9
93	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0	1.8
30	7C1	7B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	40	2	8	1.6
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	1.6
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	1.5
62	7C1	4B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	1.5
Splenic Macrophages										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	10.3
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	9.6
124	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10	4.4
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	3.4
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.2
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	1.9
97	7C1	7A-OH Cholesterol	2000	C14	-	35	60	5	0	1.9
130	7C1	Cholesteryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	1.9
32	7C1	7B-OH Cholesterol	2000	C14	DMPC	50	40	2	8	1.7
129	7C1	Cholesteryl Oleate	2000	C14	DC Chol-HCl	50	40	2	8	1.7
18	7C1	Cholesterol	2000	C14	DSPC	50	40	2	8	1.6
40	7C1	7B-OH Cholesterol	2000	C14	DC Chol-HCl	50	40	2	8	1.6
109	7C1	Cholesteryl Stearate	2000	C14	DSPC	50	40	2	8	1.5
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	1.5
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	1.5
91	7C1	7A-OH Cholesterol	2000	C14	DOPE	50	40	2	8	1.4
Liver Endothelial Cells										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
53	7C1	4B-OH Cholesterol	2000	C14	18:1 Lyso PC	50	29	11	10	3.4
130	7C1	Cholesteryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	2.8
90	7C1	7A-OH Cholesterol	2000	C14	DOPE	50	29	11	10	2.0
103	7C1	Cholesteryl Stearate	2000	C14	DOPC	50	40	2	8	1.8
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	1.6
29	7C1	7B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	29	11	10	1.6
52	7C1	7B-OH Cholesterol	2000	C14	-	35	60	5	0	1.6
57	7C1	4B-OH Cholesterol	2000	C14	DMPC	50	29	11	10	1.5
120	7C1	Cholesteryl Oleate	2000	C14	DMPC	50	29	11	10	1.5
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	1.5
5	7C1	Cholesterol	2000	C14	DMPC	50	29	11	10	1.5
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.5
126	7C1	Cholesteryl Oleate	2000	C14	O Chems PC	50	29	11	10	1.5
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	1.4
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	1.3
9	7C1	Cholesterol	2000	C14	DOTAP	50	29	11	10	1.3
Liver Hepatocytes										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	7.3
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	6.3
124	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10	3.5
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	2.7
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.0
97	7C1	7A-OH Cholesterol	2000	C14	-	35	60	5	0	1.8
130	7C1	Cholesteryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	1.5
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	1.4
132	7C1	Cholesteryl Oleate	2000	C14	DSPC	50	29	11	10	1.3
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	1.2
137	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0	1.2
9	7C1	Cholesterol	2000	C14	DOTAP	50	29	11	10	1.2
128	7C1	Cholesteryl Oleate	2000	C14	DC Chol-HCl	50	29	11	10	1.1
126	7C1	Cholesteryl Oleate	2000	C14	O Chems PC	50	29	11	10	1.1
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	1.1
41	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	29	11	10	1.0

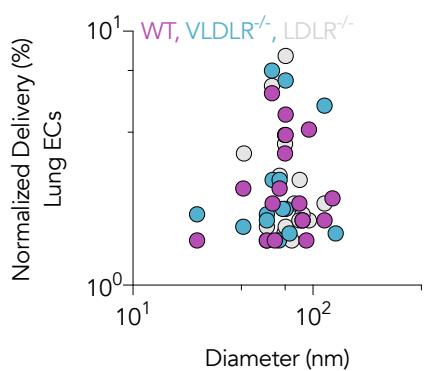
Lung Endothelial Cells VLDR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
112	7C1	Cholestryl Stearate	2000	C14	-	62	30	8	0	7.0
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	6.4
128	7C1	Cholestryl Oleate	2000	C14	DC Chol-HCl	50	29	11	10	5.1
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	3.9
77	7C1	7A-OH Cholesterol	2000	C14	18:1 Lyso PC	50	29	11	10	2.6
137	7C1	Cholestryl Oleate	2000	C14	-	62	30	8	0	2.6
81	7C1	7A-OH Cholesterol	2000	C14	DMPC	50	29	11	10	2.0
90	7C1	7A-OH Cholesterol	2000	C14	DOPE	50	29	11	10	2.0
129	7C1	Cholestryl Oleate	2000	C14	DC Chol-HCl	50	40	2	8	1.9
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.9
114	7C1	Cholestryl Stearate	2000	C14	-	80	15	5	0	1.8
93	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0	1.8
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	1.7
6	7C1	Cholesterol	2000	C14	DMPC	50	40	2	8	1.6
120	7C1	Cholestryl Oleate	2000	C14	DMPC	50	29	11	10	1.6
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	1.5
Lung Macrophages VLDR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	12.2
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	7.3
68	7C1	4B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	5.9
92	7C1	7A-OH Cholesterol	2000	C14	-	62	22	16	0	4.4
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	4.1
137	7C1	Cholestryl Oleate	2000	C14	-	62	30	8	0	3.0
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	2.8
112	7C1	Cholestryl Stearate	2000	C14	-	62	30	8	0	2.6
129	7C1	Cholestryl Oleate	2000	C14	DC Chol-HCl	50	40	2	8	2.5
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	2.1
124	7C1	Cholestryl Oleate	2000	C14	DOTAP	50	29	11	10	1.9
66	7C1	4B-OH Cholesterol	2000	C14	DC Chol-HCl	50	40	2	8	1.9
126	7C1	Cholestryl Oleate	2000	C14	O Chems PC	50	29	11	10	1.9
128	7C1	Cholestryl Oleate	2000	C14	DC Chol-HCl	50	29	11	10	1.8
113	7C1	No Cholesteorl	2000	C14	-	80	0	20	0	1.6
98	7C1	Cholestryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	1.6
Spleenic Endothelial Cells VLDR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
109	7C1	Cholestryl Stearate	2000	C14	DSPC	50	40	2	8	4.0
112	7C1	Cholestryl Stearate	2000	C14	-	62	30	8	0	3.6
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	2.6
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	2.6
81	7C1	7A-OH Cholesterol	2000	C14	DMPC	50	29	11	10	2.5
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	2.2
125	7C1	Cholestryl Oleate	2000	C14	DOTAP	50	40	2	8	2.1
48	7C1	7B-OH Cholesterol	2000	C14	-	62	30	8	0	2.1
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	2.0
114	7C1	Cholestryl Stearate	2000	C14	-	80	15	5	0	2.0
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	1.9
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	1.9
12	7C1	Cholesterol	2000	C14	O Chems PC	50	40	2	8	1.8
6	7C1	Cholesterol	2000	C14	DMPC	50	40	2	8	1.8
93	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0	1.6
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	1.6
Spleenic Macrophages VLDR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	12.7
98	7C1	Cholestryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	11.1
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	4.6
33	7C1	7B-OH Cholesterol	2000	C14	DOPC	50	29	11	10	4.5
124	7C1	Cholestryl Oleate	2000	C14	DOTAP	50	29	11	10	4.3
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.2
32	7C1	7B-OH Cholesterol	2000	C14	DMPC	50	40	2	8	2.1
18	7C1	Cholesterol	2000	C14	DSPC	50	40	2	8	2.1
7	7C1	Cholesterol	2000	C14	DOPC	50	29	11	10	2.1
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	2.0
97	7C1	7A-OH Cholesterol	2000	C14	-	35	60	5	0	1.9
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	1.7
130	7C1	Cholestryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	1.6
9	7C1	Cholesterol	2000	C14	DOTAP	50	29	11	10	1.6
137	7C1	Cholestryl Oleate	2000	C14	-	62	30	8	0	1.4
41	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	29	11	10	1.4
Liver Endothelial Cells VLDR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
137	7C1	Cholestryl Oleate	2000	C14	-	62	30	8	0	3.3
125	7C1	Cholestryl Oleate	2000	C14	DOTAP	50	40	2	8	2.1
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.0
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	1.9
70	7C1	4B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	1.9
130	7C1	Cholestryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	1.8
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	1.7
109	7C1	Cholestryl Stearate	2000	C14	DSPC	50	40	2	8	1.5
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	1.5
6	7C1	Cholesterol	2000	C14	DMPC	50	40	2	8	1.4
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	1.4
68	7C1	4B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	1.4
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.4
90	7C1	7A-OH Cholesterol	2000	C14	DOPE	50	29	11	10	1.3
98	7C1	Cholestryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	1.3
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	1.3
Liver Hepatocytes VLDR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	11.9
98	7C1	Cholestryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	4.8
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	3.0
124	7C1	Cholestryl Oleate	2000	C14	DOTAP	50	29	11	10	2.3
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	1.9
137	7C1	Cholestryl Oleate	2000	C14	-	62	30	8	0	1.5
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	1.4
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	1.3
68	7C1	4B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	1.3
110	7C1	Cholestryl Stearate	2000	C14	DOPE	50	40	2	8	1.2
8	7C1	Cholesterol	2000	C14	DOPC	50	40	2	8	1.2
130	7C1	Cholestryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	1.2
112	7C1	Cholestryl Stearate	2000	C14	-	62	30	8	0	1.2
18	7C1	Cholesterol	2000	C14	DSPC	50	40	2	8	1.1
93	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0	1.1
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	1.1

Lung Endothelial Cells LDLR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	8.0
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	6.1
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	3.6
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	3.3
137	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0	2.7
23	7C1	No Cholesterol	2000	C14	-	80	0	20	0	2.6
128	7C1	Cholesteryl Oleate	2000	C14	DC Choi-HCI	50	29	11	10	2.1
122	7C1	Cholesteryl Oleate	2000	C14	DOPC	50	29	11	10	2.1
114	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0	1.9
123	7C1	Cholesteryl Oleate	2000	C14	DOPC	50	40	2	8	1.8
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	1.8
93	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0	1.7
81	7C1	7A-OH Cholesterol	2000	C14	DMPC	50	29	11	10	1.7
5	7C1	Cholesterol	2000	C14	DMPC	50	29	11	10	1.6
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	1.5
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.5
Lung Macrophages LDLR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	11.1
9	7C1	Cholesterol	2000	C14	DOTAP	50	29	11	10	11.0
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	7.8
124	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10	3.6
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	2.9
137	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0	2.8
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.7
45	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	29	11	10	1.8
97	7C1	7A-OH Cholesterol	2000	C14	-	35	60	5	0	1.8
88	7C1	7A-OH Cholesterol	2000	C14	DC Choi-HCI	50	40	2	8	1.6
77	7C1	7A-OH Cholesterol	2000	C14	18:1 Lyso PC	50	29	11	10	1.2
21	7C1	Cholesterol	2000	C14	-	62	22	16	0	1.2
114	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0	1.2
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	1.1
23	7C1	No Cholesterol	2000	C14	-	80	0	20	0	1.1
18	7C1	Cholesterol	2000	C14	DSPC	50	40	2	8	1.0
Spleenic Endothelial Cells LDLR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
109	7C1	Cholesteryl Stearate	2000	C14	DSPC	50	40	2	8	5.5
6	7C1	Cholesterol	2000	C14	DMPC	50	40	2	8	3.4
56	7C1	4B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	40	2	8	2.8
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	2.7
70	7C1	4B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	2.3
40	7C1	7B-OH Cholesterol	2000	C14	DC Choi-HCI	50	40	2	8	2.2
20	7C1	Cholesterol	2000	C14	DOPE	50	40	2	8	2.1
62	7C1	4B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	2.0
18	7C1	Cholesterol	2000	C14	DSPC	50	40	2	8	2.0
95	7C1	7A-OH Cholesterol	2000	C14	-	80	15	5	0	1.9
114	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0	1.9
88	7C1	7A-OH Cholesterol	2000	C14	DC Choi-HCI	50	40	2	8	1.8
32	7C1	7B-OH Cholesterol	2000	C14	DMPC	50	40	2	8	1.7
12	7C1	Cholesterol	2000	C14	O Chems PC	50	40	2	8	1.7
107	7C1	Cholesteryl Stearate	2000	C14	DC Choi-HCI	50	40	2	8	1.6
110	7C1	Cholesteryl Stearate	2000	C14	DOPE	50	40	2	8	1.6
Spleenic Macrophages LDLR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	4.4
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	3.7
112	7C1	Cholesteryl Stearate	2000	C14	-	62	30	8	0	3.3
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	3.2
84	7C1	7A-OH Cholesterol	2000	C14	DOPC	50	40	2	8	2.8
23	7C1	No Cholesterol	2000	C14	-	80	0	20	0	2.6
25	7C1	Cholesterol	2000	C14	-	35	35	30	0	2.4
128	7C1	Cholesteryl Oleate	2000	C14	DC Choi-HCI	50	29	11	10	2.4
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	2.2
125	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	40	2	8	2.1
137	7C1	Cholesteryl Oleate	2000	C14	-	62	30	8	0	2.1
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	1.8
124	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10	1.8
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	1.8
129	7C1	Cholesteryl Oleate	2000	C14	DC Choi-HCI	50	40	2	8	1.8
114	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0	1.6
Liver Endothelial Cells LDLR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
41	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	29	11	10	7.2
89	7C1	7A-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.7
35	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	29	11	10	2.4
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	2.3
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.2
130	7C1	Cholesteryl Oleate	2000	C14	Biotinyl PE	50	29	11	10	2.1
103	7C1	Cholesteryl Stearate	2000	C14	DOPC	50	40	2	8	1.7
86	7C1	7A-OH Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.7
90	7C1	7A-OH Cholesterol	2000	C14	DOPE	50	29	11	10	1.5
53	7C1	4B-OH Cholesterol	2000	C14	18:1 Lyso PC	50	29	11	10	1.4
129	7C1	Cholesteryl Oleate	2000	C14	DC Choi-HCI	50	40	2	8	1.4
29	7C1	7B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	29	11	10	1.4
94	7C1	No Cholesterol	2000	C14	-	80	0	20	0	1.3
36	7C1	7B-OH Cholesterol	2000	C14	DOTAP	50	40	2	8	1.2
122	7C1	Cholesteryl Oleate	2000	C14	DOPC	50	29	11	10	1.2
118	7C1	Cholesteryl Oleate	2000	C14	16:0 - 18:1 PC	50	29	11	10	1.2
Liver Hepatocytes LDLR-/-										
LNP #	Lipomer	Cholesterol	PEG MW	PEGChain	Helper Lipid	Lipomer Mole %	Cholesterol Mole %	PEG Mole %	Helper Lipid Mole %	Normalized Delivery (%)
46	7C1	7B-OH Cholesterol	2000	C14	DOPE	50	40	2	8	7.7
98	7C1	Cholesteryl Stearate	2000	C14	18:1 Lyso PC	50	29	11	10	3.6
124	7C1	Cholesteryl Oleate	2000	C14	DOTAP	50	29	11	10	2.5
10	7C1	Cholesterol	2000	C14	DOTAP	50	40	2	8	2.5
42	7C1	7B-OH Cholesterol	2000	C14	Biotinyl PE	50	40	2	8	2.3
59	7C1	4B-OH Cholesterol	2000	C14	DOPC	50	29	11	10	2.3
55	7C1	4B-OH Cholesterol	2000	C14	16:0 - 18:1 PC	50	29	11	10	2.2
138	7C1	No Cholesterol	2000	C14	-	80	0	20	0	2.2
126	7C1	Cholesteryl Oleate	2000	C14	O Chems PC	50	29	11	10	1.9
93	7C1	7A-OH Cholesterol	2000	C14	-	62	30	8	0	1.7
114	7C1	Cholesteryl Stearate	2000	C14	-	80	15	5	0	1.7
24	7C1	Cholesterol	2000	C14	-	80	15	5	0	1.7
11	7C1	Cholesterol	2000	C14	O Chems PC	50	29	11	10	1.6
120	7C1	Cholesteryl Oleate	2000	C14	DMPC	50	29	11	10	1.5
13	7C1	Cholesterol	2000	C14	DC Choi-HCI	50	29	11	10	1.5
69	7C1	4B-OH Cholesterol	2000	C14	DOPE	50	29	11	10	1.4

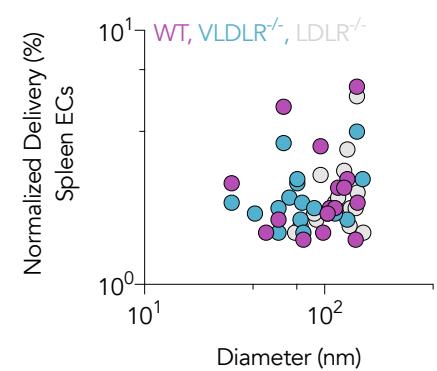
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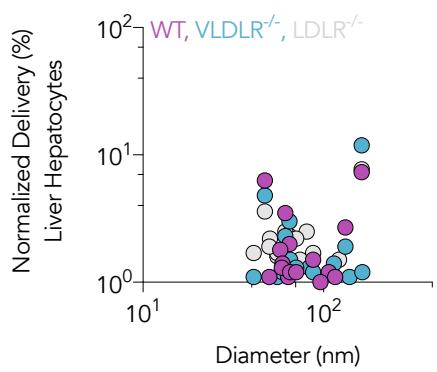
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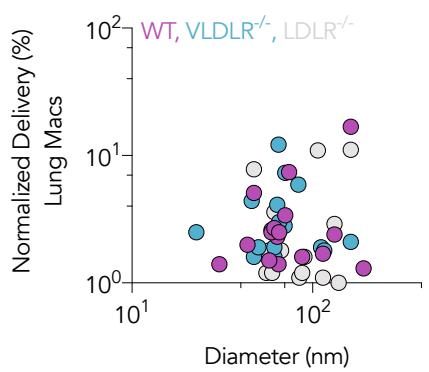
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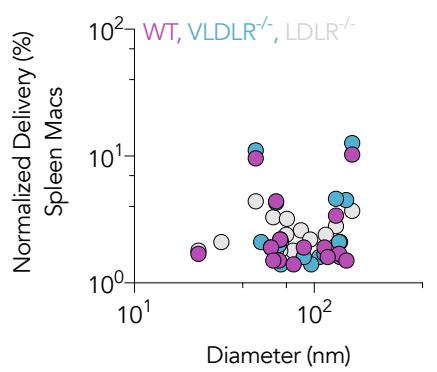
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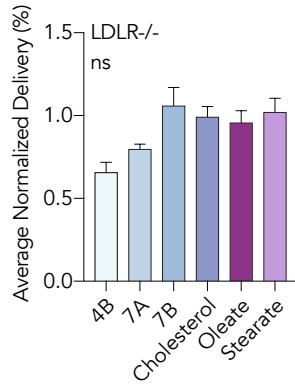


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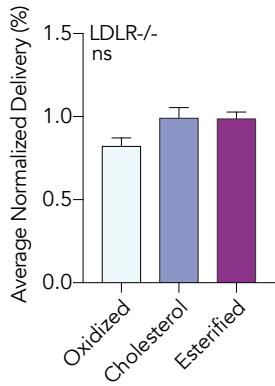
	Size vs. WT	Size vs. VLDLR ^{-/-}	Size vs. LDLR ^{-/-}
Liver ECs	.113	.446	.082
Lung ECs	.001	.012	.054
Spleen ECs	.016	.114	.122
Liver Hepatocytes	.115	.132	.426
Lung Macs	.134	.011	.108
Spleen Macs	.011	.046	.064

↑
↔ R²

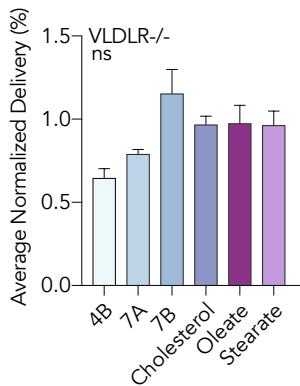
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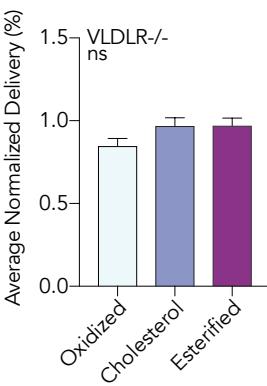
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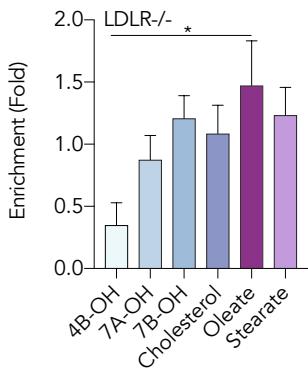
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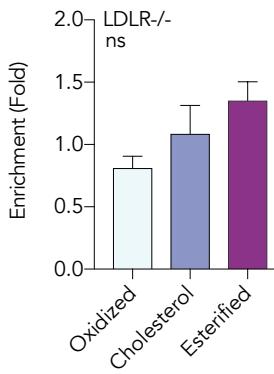
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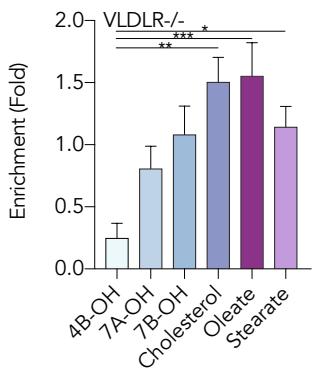
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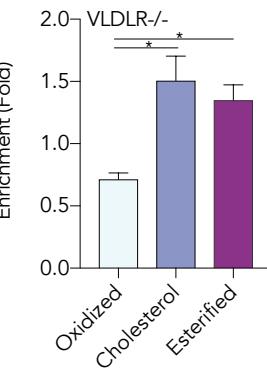
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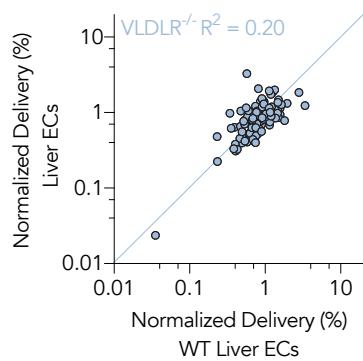


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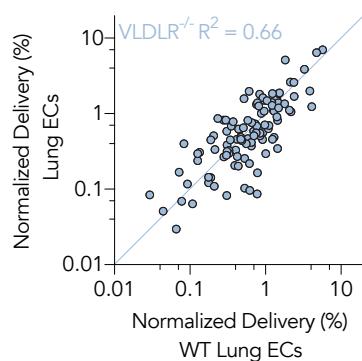


Supplementary Figure 3. Normalized delivery in **(A-F)** VLDLR^{-/-} mice and **(G-L)** and LDLR^{-/-} mice plotted against normalized delivery in WT mice for endothelial cells (ECs), macrophages (Macs), and Hepatocytes.

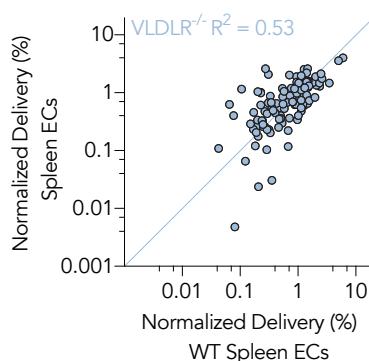
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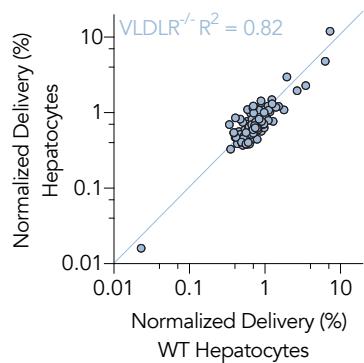
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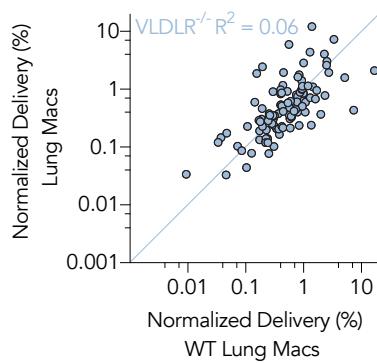
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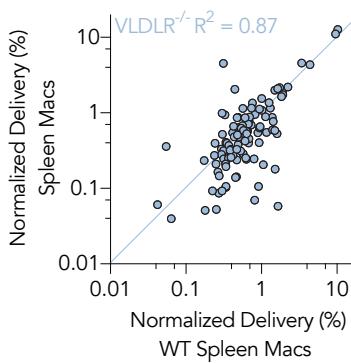
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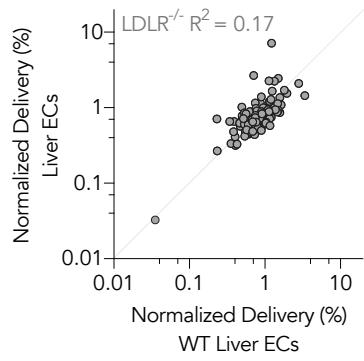
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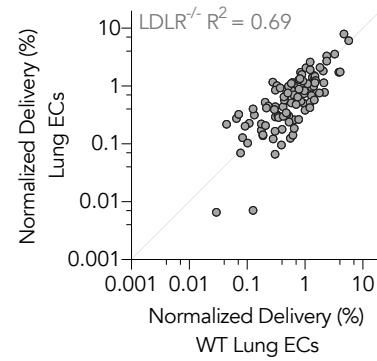
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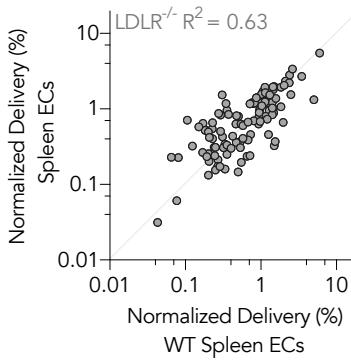
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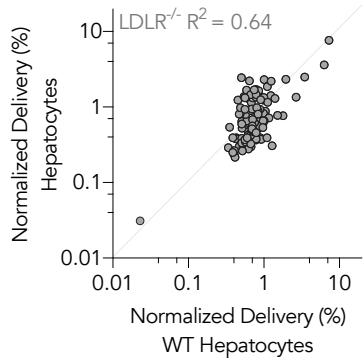
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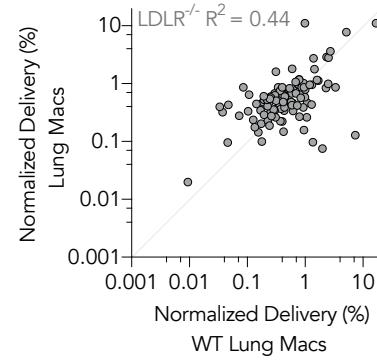
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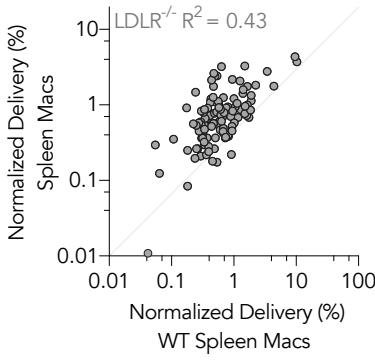
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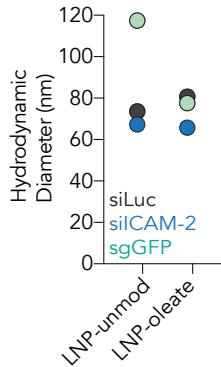


L



Supplementary Figure 4. **(A)** LNP-unmod and LNP-oleate formed small, stable LNPs when formulated to carry **(B)** modified sgRNA targeting the GFP locus or **(C)** modified siRNA against ICAM-2. **(D)** Normalized mouse weights 0-5 days post sgRNA containing LNP-unmod and LNP-oleate injection. **(E)** Normalized mouse weights for 0, 1, and 2 days post siRNA containing LNP-unmod and LNP-oleate injection. Mouse weights are always normalized to mouse weight immediately before injection.

A



B

e-sgGFP: 5' gggsgsCGAsGsGfsAfGsCfUGfUfUCAf
CfCGgUUUUAGagcuagaaaugcaaGUUa
AaAuAaggcuaGUccGUUAucAAcsususgs
asasasasasgugGscascscsgsasgsuscgsg
susgscsusususu 3'

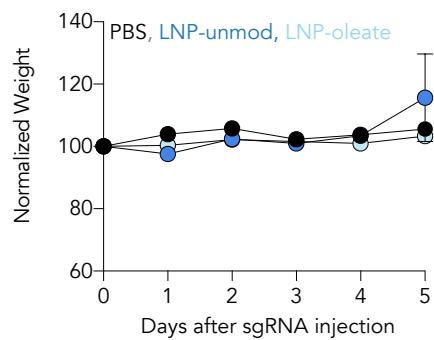
A, G, U, C: RNA nucleotide
a, g, u, c: 2'-O-Methyl nucleotide
Af, Gf, Uf, Cf: 2'-Fluoro modification
s: phosphorothioate

C

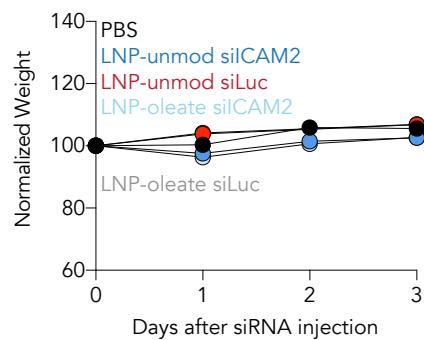
siLCAM-2 sense: 5' - AGGAcGGucucACuuuuc dT sdT - 3'
siLCAM-2 antisense: 5' - GAAAAGUuGAGACCGUCCU dT sdT - 3'

A, G, U, C: RNA nucleotide
dT: deoxy-T
a, g, u, c: 2'-O-Methyl nucleotide
s: phosphorothioate

D



E



Supplementary Table 1. Calculation showing the # of *in vivo* data points.

# of LNPs Tested + Naked BC	# of Cell Types Tested	# of Mouse Models	Total Data Points
111	6	3	1998

Supplementary Table 2. Significance data for Figure 2D.

WT Mice (Normalized Delivery) Fig 2D			
Comparison	Significant?	Summary	Adjusted P Value
7A vs. 4B	No	ns	0.6595
7B vs. 4B	Yes	**	0.0013
Cholesterol vs. 4B	No	ns	0.1688
Oleate vs. 4B	Yes	**	0.0013
Stearate vs. 4B	Yes	***	0.0005
7B vs. 7A	Yes	*	0.0375
Cholesterol vs. 7A	No	ns	0.7502
Oleate vs. 7A	Yes	*	0.0375
Stearate vs. 7A	Yes	*	0.0156
Cholesterol vs. 7B	No	ns	0.27
Oleate vs. 7B	No	ns	0.9965
Stearate vs. 7B	No	ns	0.9755
Oleate vs. Cholesterol	No	ns	0.27
Stearate vs. Cholesterol	No	ns	0.1603
Stearate vs. Oleate	No	ns	0.9755

Supplementary Table 3. The strain, sex, and age of each mouse as well as the number of mice used in each experiment and the type of procedure done on each group of mice.

Strain	Sex	Procedure	# of mice (N)	Age
C57BL/6	F	IV Injection (Inj.) LNPs	4	5-8 weeks
VLDLR/-	F	IV Inj. LNPs	3	5-8 weeks
LDLR/-	F	IV Inj. LNPs	3	5-8 weeks
Strain	Sex	Procedure	N	Age
C57BL/6	F	IV Injection (Inj.) PBS	4	5-8 weeks
C57BL/6	F	IV Inj. LNP-unmod siICAM	4	5-8 weeks
C57BL/6	F	IV Inj. LNP-oleate siICAM	4	5-8 weeks
C57BL/6	F	IV Inj. LNP-unmod siLuc	4	5-8 weeks
C57BL/6	F	IV Inj. LNP-oleate siLuc	4	5-8 weeks
Strain	Sex	Procedure	N	Age
Cas9-GFP	F	IV Injection (Inj.)PBS	4	5-8 weeks
Cas9-GFP	F	IV Inj. sgGFP LNP-unmod	4	5-8 weeks
Cas9-GFP	F	IV Inj. sgGFP LNP-oleate	4	5-8 weeks