

## Supplementary table

**Table S1** A collection table of techniques and methods used for purification and characterization of surface-engineered LNPs

Classes	Techniques and methods	Applications
Purification	Dialysis	Buffer exchange; Removal of small molecules, peptides, and antibodies
	Ultracentrifugation	Buffer exchange; Removal of small molecules, peptides, antibodies, and free siRNA
	SEC	Removal of antibodies
Physicochemical characterization	DLS	Measurement of hydrodynamic size, PDI, and zeta potential of LNPs
	SAXS	Measurement of size, lamellarity, and internal structure of LNPs
	TEM and cryo-TEM	Measurement of size, morphology, lamellarity, and internal structure of LNPs
	Gel electrophoresis	Validation of conjugated DNA, aptamers, and antibodies
	BCA assay	Validation of conjugated peptides and antibodies
	Peterson-Lowry assay	Validation of conjugated peptides and antibodies
	Fluorescence and chemiluminescence assays	Validation of conjugated peptides and antibodies
Functional characterization	Tritium-labeling	Measurement of HA concentration
	Lectin affinity assay	Validation of binding activity of glycolipids
	Cell-free ASGPR competition method	Validation of binding activity of GalNAc-lipids
	Hydroxyapatite binding assay	Validation of binding activity of alendronate-lipids
	ELISA	Validation of binding activity of antibodies
	Flow cytometry	Evaluation of cellular binding and uptake of LNPs
	CLSM	Evaluation of cellular binding and uptake LNPs; Intracellular trafficking of LNPs
<i>Ex vivo</i> bone model	Validation of binding activity of alendronate-lipids	

SEC, size exclusion chromatography; DLS, dynamic laser scattering; SAXS, small-angle X-ray scattering; TEM and cyro-TEM, transmission electron microscopy and cryogenic transmission electron microscopy; BCA assay, bicinchoninic acid assay; ELISA, enzyme-linked immunosorbent assay; CLSM, confocal laser scanning microscopy

**Table S2** Surface-engineered LNPs for targeted nucleic acid delivery

Targeted organ/ cell type	Ligand type	Ligand	Target	Payload	Reference
Liver/hepatocytes	Small molecule	GalNac	ASGPR	FVII siRNA	Akinc et al. 2010
Liver/hepatocytes	Small molecule	GalNac	ASGPR	Base editing mRNA/sgRNA	Kasiewicz et al. 2023
Liver/hepatocytes	Small molecule	GalNac	ASGPR	FVII and HBV siRNA	Sato et al. 2017
Liver/hepatic stellate cells	Small molecule	Anisamide	Sigma receptor	HSP47 siRNA	Han et al. 2023
Liver/macrophages	Small molecule	Mannose	Mannose receptor	TNF $\alpha$ siRNA	Wang et al. 2023
Liver/hepatic stellate cells	Peptide	pPB peptide	PDGFR- $\beta$	gp46 siRNA	Jia et al. 2018
Liver/hepatic stellate cells	Peptide	pPB peptide	PDGFR- $\beta$	HMGB1 siRNA	Zhang et al. 2020
Spleen	DNA	G-rich DNA motifs	class A scavenger receptor	STING DNA, Luc siRNA and mRNA	Sinegra et al. 2021
Spleen/CD3+ T cells	Antibody	Anti-CD3 antibody	CD3	IL-6 shRNA- and anti-CD19-CAR-encoded pDNA	Zhou et al. 2022
Spleen/CD4+ T cells	Antibody	Anti-CD4 antibody	CD4	Luc and Cre mRNA	Tombácz et al. 2021
Spleen/CD5+ T cells	Antibody	Anti-CD5 antibody	CD5	FAP CAR mRNA	Rurik et al. 2022

Targeted organ/ cell type	Ligand type	Ligand	Target	Payload	Reference
Spleen/DEC205 + DCs	Antibody	Anti-DEC205 scFv	DEC205	CD40, CD80, and CD86 siRNA	Katakows ki et al. 2015
Spleen/virus-spe cific T cells	pMHCI	Virus-specific pMHCI molecule	NR	eGFP, Luc, and VHH mRNA	Su et al. 2022
Spleen	Lipid	Aninoic lipid (e.g., 18PA)	NR	Luc, Cre, Cas9 mRNA and sgRNA; Cas9/sgRNA ribonucleopr oteins	Cheng et al. 2018
Lung	Small molecule	Mannose	Mannose receptor	GTSE1 siRNA	Jin et al. 2023
Lung/airway epithelial cell	Peptide	(NNGGGGCS ERSMNFC) peptide	ICAM-1	TSLP siRNA	Zhang et al. 2022
Lung	Antibody	Anti-PV1 antibody	PV1	Luc mRNA	Li et al. 2020
Lung	Lipid	Cationic lipid (e.g., DOTAP)	NR	Luc, Cre, Cas9 mRNA and sgRNA; Cas9/sgRNA ribonucleopr oteins	Cheng et al. 2018
LNCaP tumor cells	Small molecule	Glu-urea-Lys	PSMA	AR siRNA	Lee et al. 2016
Ovarian tumor cells	Polymer	HA	CD44	eIF3c and PLK1 siRNA	Singh et al. 2021

Targeted organ/ cell type	Ligand type	Ligand	Target	Payload	Reference
Glioblastoma multiforme cells	Polymer	HA	CD44	PLK1 siRNA	Cohen et al. 2015
Tumor endothelial cells	Peptide	RGD peptide	$\alpha\text{v}\beta\text{3}$	DLL4 siRNA	Sakurai et al. 2018
HepG2 tumor cells	Peptide	RGD peptide	$\alpha\text{v}\beta\text{3}$	PLK1 siRNA	Guo et al. 2021
Hep3B tumor cells	Peptide	Epi-1 peptide	EpCAM	PLK1 siRNA	Sakurai et al. 2017
Ovarian tumor SKOV-3 cells	Peptide	Epi-1 peptide	EpCAM	PLK1 siRNA	Sakurai et al. 2020
Tumor cells	Peptide	tLyp-1 peptide	NRP-1	KRAS siRNA	Anthiya et al. 2023
Tumor endothelial cells	Peptide	RGD peptide	$\alpha\text{v}\beta\text{3}$	VEGFR2 siRNA	Sakurai et al. 2016
Hepatocellular carcinoma cells	Peptide	CTCE-9908 peptide	CXCR4	p53 mRNA	Xiao et al. 2022
Mantle cell lymphoma (MCL) cells	Antibody	Anti-CD38 antibody	CD38	cyclin D1 siRNA	Weinstein et al. 2016
Multiple myeloma cells	Antibody	Anti-CD38 antibody	CD38	CKAP5 siRNA	Tarab-Rav ski et al. 2023
Ovarian tumor cells	Antibody	Anti-EGFR antibody	EGFR	PLK1 siRNA	Rosenblu m et al. 2020
Head and neck cancer cells	Antibody	Anti-EGFR antibody	EGFR	E6 siRNA	Kampel et al. 2021
Tumor myeloid cells and cancer cells	Antibody	Anti-PD-L1 antibody	PD-L1	HO1 siRNA	Yong et al. 2022
Osteoblast	Aptamer	CH6 aptamer	NR	Plekho1 siRNA	Liang et al. 2015

Targeted organ/ cell type	Ligand type	Ligand	Target	Payload	Reference
Brain	Peptide	RVG-9r peptide	Acetylcholine receptor	Mutant ataxin-3 siRNA	Conceição et al. 2016
BBB endothelium	Antibody	Anti-VCAM-1 antibody	VCAM-1	IL-10 mRNA	Jia et al. 2023
Retina	Peptide	MH42 peptide	NR	Cre and GFP mRNA	Herrera-B arrera et al. 2023
Retina	Modified PEG-lipids	Carboxyester modified PEG-lipids	NR	Cre, Cas9 mRNA and sgAi9	Gautam et al. 2023
Bone	Small molecule	Alendronate	Hydroxyapatite	Luc, GFP, and BMP-2 mRNA	Xue et al. 2022
M2 polarized macrophages	Small molecule	Mannose	Mannose receptor	IL-10 mRNA	Gao et al. 2023
Keratinocytes	Peptide	A5G33 peptide	NR	Anti-miR- 107	Li et al. 2018
HSCs	Antibody	Anti-CD117 antibody	CD117	Cre, Luc, ABE, and PUMA mRNA	Breda et al. 2023
HSCs	Antibody	Anti-CD117 antibody	CD117	CD45 siRNA and Cre mRNA	Shi et al. 2023
Vascular endothelial cells	Antibody	Anti-VCAM-1 antibody	VCAM-1	RelA siRNA	He et al. 2022
Gut-homing leukocytes	Antibody	Anti-high-affin ity conformation of integrin $\alpha 4\beta 7$	High-affinity conformation of integrin $\alpha 4\beta 7$	IFN- $\gamma$ siRNA	Dammes et al. 2021

Targeted organ/ cell type	Ligand type	Ligand	Target	Payload	Reference
Leukocytes	Antibody	Anti CD44, CD34, Ly6C, CD3, CD4, CD25, CD29, and Itgb7 antibodies	CD44, CD34, Ly6C, CD3, CD4, CD25, CD29, and Itgb7	siRNA	Kedmi et al. 2018
Ly6c+ inflammatory leukocytes	Antibody	Anti-Ly6c antibody	Ly6C	IL-10 mRNA	Veiga et al. 2018
Targeted organ/cell type	Ligand type	Ligand	Target	Payload	Reference
CD4+ and CD8+ T cells	Antibody	Anti-integrin $\beta$ 7 antibody	Integrin $\beta$ 7	CD45 siRNA	Ramishetti et al. 2020
CD4+ T cells	Antibody	Anti-CD4	CD4	CD45 siRNA	Ramishetti et al. 2015
Lymphatic endothelial cells	Antibody	Anti-podoplanin antibody	Podoplanin	PD-L1 siRNA	Sakurai et al. 2022

FVII, factor VII; HSP47, heat shock protein 47; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; gp46, glycoprotein 46; PDGFR- $\beta$ , platelet-derived growth factor receptor beta; HMGB1, high mobility group box 1; STING, stimulator of interferon genes; IL-6, interleukin 6; CAR, chimeric antigen receptor; FAP, fibroblast activation protein; eGFP, enhanced green fluorescent protein; Luc, luciferase; TSLP, thymic stromal lymphopoietin; AR, androgen receptor; eIF3c, eukaryotic translation initiation factor 3 subunit c; PLK1, polo like kinase 1; DLL4, delta like canonical Notch ligand 4; NRP1, neuropilin 1; KRAS, kirsten rat sarcoma virus; VEGFR2, vascular endothelial growth factor receptor 2; CKAP5, cytoskeleton associated protein 5; HO1, heme oxygenase 1; Plekh01, pleckstrin homology domain containing O1; IL-10, interleukin 10; BMP-2, bone morphogenetic protein 2; ABE, adenine base editor; PUMA, p53 up-regulated modulator of apoptosis; IFN- $\gamma$ , interferon  $\gamma$ ; NR, not reported

**Table S3** Surface-engineered LNPs for other purposes

Ligand type	Ligand	Payload	Purpose	Reference
Polymer	Polysarcosine	Luc and EPO mRNA	Reducing immunostimulatory response, proinflammatory cytokine secretion, and reduced complement activation; Inducing higher protein secretion	Nogueira et al. 2020
Polymer	Polysarcosine	Luc and Thy1.1 mRNA	Enhancing transfection efficiency in vitro	Wilhelmy et al. 2023
Small molecule	GalNAc	siFVII and HBV siRNA	Reducing toxicity and neutrophilic inflammation	Sato et al. 2017
Small molecule	Mannose	RSV F protein saRNA	Improving immunogenicity and antibody response of RNA vaccines; improving onset time of antibody response	Goswami et al. 2019
Small molecule	Mannose	Influenza hemagglutinin-encoded saRNA	Improving immunogenicity and antibody response of RNA vaccines; improving onset time of antibody response	Goswami et al. 2021
Peptide	KALA peptide	Luc and OVA mRNA	Avoiding the activation of pathways which down-regulates the cellular mRNA translation	Tateshita et al. 2019
Peptide	PAM3 peptide	OVA mRNA	Immune adjuvant	Lee et al. 2020
Peptide	cY peptide	MRTF-B siRNA	Increasing encapsulation efficiency; enhancing endosomal escape	Sanghani et al. 2021
Peptide	MTAS-NLS peptide	IL-6 shRNA and anti-CD19-CAR pDNA	Helping the plasmid gene to enter the nucleus; increasing transfection efficiency	Zhou et al. 2022

Luc, luciferase; EPO, erythropoietin; HBV, hepatitis B virus; RSV F protein, respiratory syncytial virus fusion protein; saRNA, self-amplifying RNA; OVA, ovalbumin; MRTF-B, myocardin-related transcription factor B; IL-6, interleukin 6; shRNA, short hairpin RNA; CAR, chimeric antigen receptor