Electronic Supplementary Material (ESI) for Biomaterials Science.

Supporting Information

Non-viral delivery of the CRISPR/Cas system: DNA versus RNA versus RNP

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Content

Table 1. Delivery systems of Cas9 plasmids.

Type of delivery systems	Main components	Target gene(s)	Target organ(s) or cell types in vivo	Administration route	Ref.
Polymeric delivery systems	Fluorinated branched PEI, RGD-R8-PEG-HA	MTH1	Tumor	I.V.	1
	LC09-functionalized PEG-PEI-Cholesterol, LC09-PEG2000-DSPE	VEGFA	Orthotopic osteosarcoma	I.V.	2
	PEI, HA, and iRGD	Ptpn2	Tumor	I.V.	3
	Semiconducting polymer brush, alkyl chains, PEG, and fluorinated PEI	GFP, MTH1	Tumor	I.T.	4
	Semiconducting polymer, PEG2000, and PEI	HDR: GFP reporter	Subcutaneous HeLa cells pretreated with pSPN	Ex vivo	5
	PEI-β-cyclodextrin	RHBDF1, HBB	×	×	6
	branched PEI	Slc26a4	×	×	7
	PEG-PLGA, BHEM-Chol	BCR-ABL	Chronic myeloid leukemia	I.V.	8
	PEG-PLGA, BHEM-Chol	CD80, CD86, and CD40	Dendritic cells	I.V.	9
	PEG-PLGA, BHEM-Chol	Ntn1	Macrophages, monocytes	I.V.	10
	PEG5K-PLGA11K, PLGA11K, BHEM-Chol or DOTAP	B220, BAFFR	B cells	I.V.	11
	PEG-PLGA, PLGA, and BHEM-Chol	NE	Neutrophils	I.V.	12
	PLGA, chitosan	GFP	×	×	13
	PLGA, lecithin, DSPE-PEG-cRGD, DSPE-PEG-biotin, DC-cholesterol, and C3F8 filled microbubbles	MGMT	Glioblastoma	I.V.	14
	Hyperbranched poly(amide-amine)-PBAE, linear PBAE	HPV16 E7	Tumor	Peritumoral injection	15
	PBAE	Cdk5	Tumor	I.T.	16
	Reducible branched PBAE	GFP	×	×	17
	PBAE	GFP, iRFP	×	×	18

	Cholesterol-terminated ethanolamine-aminated PGEA	Fbn1	Aorta	I.V. in eye canthus vein	19
	Ethanolamine-modified PGEA, heparin	Survivin	Orthotopic hepatocellular carcinoma	I.V.	20
	Chitosan, β-galactose-carrying lactobionic acid	VEGFR2	Tumor	I.V.	21
	Chitosan-mPEG	×	×	×	22
	Fluorinated polycations	Survivin	Tumor	I.V.	23
	PBA-functionalized polyaminoglycosides	Survivin	Tumor	I.V.	24
	Poly(disulfide)s	CCNE1	Liver	I.V.	25
	α-helical polypeptide PPABLG	Plk1	Tumor	I.T.	26
	Lactose-derived branched cationic biopolymer	Survivin	Orthotopic hepatocellular carcinoma	I.V.	27
	Quaternary ammonium-terminated poly(propylene oxide), Pluronic F127	HPV E7	Tumor	I.T.	28
	Alginate	GFP	×	×	29
	Pristine 4-arm polyrotaxane, NCAM or PipB peptide	DMD	×	×	30
Lipidic delivery systems	iLY1809, cholesterol, DSPC, DMG-PEG2K	Plk1	Tumor	I.T.	31
	DOTAP, cholesterol, DOPE, PEG2K-C16 ceramide	HPV E6 and E7	Tumor	I.V.	32
	DOTAP, cholesterol, DOPE, DSPE-PEG2K, protamine	Plk1	Tumor	I.T.	33
	DOTAP, DOPE, DSPE-PEG2K	Knock-in: Idua	Lung, liver and heart (neonatal MPS I mice)	I.V. in superficial temporal vein	34
	DOTAP, cholesterol, R8-dGR-DSPE-PEG2K	HIF-1α	Tumor	I.V.	35
	DOTAP, DOPE, DSPE-PEG2000-NH2 or DSPE-PEG2000-pardaxin peptide	CDC6	Subcutaneous tumor and orthotopic liver tumor	I.V.	36
	DOTAP, cholesterol, DOPE, Chol-PEG2K or DSPE-PEG2K	GFP	×	×	37
	Amino lipids	GFP	×	×	38

	Medium chain triglycerides, DOTAP, DOPE, DSPE-PEG2K	Knock-in: Idua	×	×	39
	DOTAP, TQ-BPN	HPV18 E6 and E7	Tumor	I.T.	40
	PC, cholesterol, DOTAP, DSPE-PEG peptide	HuR	×	×	41
Inorganic and inorganic/ organic hybrid delivery systems	SPION, DOPA-PLys-PEG-Flu, DOPA-PLys-PEG-RVG	BACE1	Brain	I.V.	42
	MSN, PAMAM-Apt	EGFR	Hepatocellular carcinoma	I.V.	43
	Au nanorods, galactose-modified branched PEI	Fas	Liver	I.V.	44
	Au nanorods, polystyrene sulfonate, β-cyclodextrin-PEI , biguanidyl adamantane	PD-L1	Tumor	I.T.	45
	Photocleavable electropositive PEG, UV-emitting upconversion nanoparticles	Plk1	Tumor	I.T.	46
	TAT peptide-modified Au nanoparticles, DOTAP, cholesterol, DOPE, DSPE-PEG2K	Plk1	Tumor	I.T.	47
	TAT peptide-modified Au nanoclusters, DOTAP, cholesterol, DOPE, DSPE-PEG2K	Plk1	Tumor	I.T.	48
	Au nanorods, polystyrene sulfonate, β-cyclodextrin-PEI with or withour galactose	Fas	Liver, tumor, muscle	I.V., I.M., peritumoral injection	49
	Magnetic nanoparticles, PEI	TLR-3 reporter	×	×	50
	Au nanoclusters, protamine	HPV18 E7	×	×	51
	UiO-66, p(HEMA), p(NIPAM)	GFP	×	×	52
	Cy5.5-MSNs-NLS, poly(dimethyldiallylammonium chloride)	Knock-in: GFP-tag	×	×	53
	MSN, DOTAP, cholesterol, DOPE, DSPE-PEG2K	GFP-RFP reporter	×	Intrastriatal injection	54
	N–Zn-doped carbon dots	GFP	×	×	55
	Vitamin D3-functionalized carbon dots	GFP	×	×	56
	ZIF-C, EGCG	RPSA	×	×	57
	ErDy nanosheets	Plk1	Tumor	I.V.	58
	$CaCO_3$, protamine, AS1411 aptamer and TAT-NLS-HA	CTNNB1	×	×	59

	$CaCO_3$, SiO2, poly-L-arginine, dextran sulfate	tdTomato	×	×	60
	$CaCO_3$, protamine, AS1411 aptamer and NLS-alginate	FAK	×	×	61
	$CaCO_3$, CaP, protamine, AS1411 aptamer and biotin-carboxymethyl chitosan	CDK11	×	×	62
	$CaCO_3$, protamine, AS1411 aptamer and TAT-carboxylmethyl chitosan	CTNNB1	×	×	63
Bio-derived vesicles	Tumor-derived exosomes	PARP-1	Tumor	I.V., I.T.	64
	CAR-EVs	MYC	Tumor	I.V., I.T.	65
	Exosome-liposome hybrid NPs	CTNNB1	×	×	66
Protein-based delivery systems	Protamine, KALA, AS1411 aptamer, carboxylmethyl chitosan	CDK11	×	×	67
	Histone, KALA, HA, AS1411 aptamer-HA	PPM1D	×	×	68
	Bispecific antibody derivatives-chromatin	DPH1	×	×	69
	HSA, stearyl PEI	PD-L1	×	×	70

Table 2. Delivery systems of Cas9 mRNA and sgRNA.

Type of delivery systems	Main components	Target gene(s)	Target organ(s) or cell types in vivo	Administration route	Ref.
Polymeric delivery systems	PLGA, DOTAP, DOPE, cholesterol and DSPE-PEG2K	GFP	×	×	71
	PEG5K-b-PLGA11K, PLGA11K, and BHEM-Chol	CD40	Dendritic cells	I.V.	72
	T20-g-PCL, PEI	EGFP	×	×	73
	PEG-PAsp(DET)	Ai9 reporter	Brain	Intrabrain	74
	Poly(disulfide)s	CCNE1	×	×	25
Lipidic delivery systems	306Oi10/cholesterol/DOPE/C14-PEG2K (molar ratio 35/46.5/16/2.5)	LoxP locus	Liver	I.V.	75
	306-O12B/cholesterol/DOPC/DMG-PEG2K (molar ratio 50/38.5/10/1.5)	Angptl3	Liver	I.V.	76
	Ionizable lipid/cholesterol/DSPC/DMG-PEG/DSPE-PEG (molar ratio 50/10.5/38/1.4/0.1), anti-human EGFR antibody	Plk1	Tumor (orthotopic glioblastoma and disseminated ovarian tumor)	I.C. and I.P.	77
	BAMEA-O16B/cholesterol/DOPE/DSPE-PEG2K (weight ratio 16/8/4/1)	Pcsk9	Liver	I.V.	78
	4A3-SC8/cholesterol/DOPE/DMG-PEG (molar ratio 38.5/30/30/1.5)	HDR: BFP to GFP	Tumor	I.V.	79
	7C1/cholesterol/18:1 Lyso PC or DOPE/C14-PEG2K (weight ratio 2/0.52/0.28/0.13)	ICAM2	Splenic endothelial cells and hepatocytes	I.V.	80
	LP01/cholesterol/DSPC/DMG-PEG2K (molar ratio 45/44/9/2)	Ttr	Liver	I.V.	81
	400-O16B-3/cholesterol/DOPE/DSPE-PEG2K (weight ratio 16/4/1/1)	Nrsf	×	×	82
	75-OcholB/DOPE (weight ratio 1/1)	EGFP	×	×	83
	ZA3-Ep10/cholesterol/PEG-lipid (molar ratio 50/38.5/0.5)	LoxP locus	Liver	I.V.	84
	SORT lipids/5A2-SC8/cholesterol/DOPE/DMG-PEG2K	loxP, PTEN, Pcsk9	Spleen, liver and lung	I.V.	85
	9A1P9/helper lipids/cholesterol/DMG-PEG2K	tdTomato, PTEN	Spleen, liver and lung	I.V.	86
	C12-200/cholesterol/DOPE/C14-PEG2K/arachidonic acid (weight ratio 50/20/10/10/10)	HDR: Fah	Liver	I.V.	87
	MPA-A or MPA-Ab/cholesterol/DOPE/DMG-PEG2K (molar ratio 20/40/30/0.75)	EGFP	Tumor	I.V. and I.T.	88

	TT3/cholesterol/DOPE/DMG-PEG2K (molar ratio 15/45/25/0.75)	GFP, Pcsk9	Liver	I.V.	89
	PBA-BADP	GFP, HPV18E6	×	×	90

Table 3. Delivery systems of Cas9 RNPs.

Type of delivery systems	Main components	Target gene(s)	Target organ(s) or cell types in vivo	Administration route	Ref.
Polymeric delivery systems	Crosslinked polymer nanocapsule	tdTomato reporter	Murine retinal pigment epithelium and skeletal muscle	Subretinal injection, I.M.	91
	AD-PAMAM, CD-PEI, AD-PEG, AD-PEG-TAT	DMD	×	×	92
	Poly(disulfide)s	CCNE1	×	×	25
	PEO-b-PDMAEMA-b-PnBMA	mCherry reporter	×	×	93
	AD-disulfide-guanidyl, β-CD-PEI, microneedle patch	NLRP3	Subcutaneous keratinocytes and immune cells	Topically on the skin	94
	PLGA	γ-globin	×	×	95
	AD and β-CD conjuagted PBAP	mCherry	×	×	96
	Poly(aspartic acid-(2-aminoethyl disulfide)-(4-imidazolecarboxylic acid))−PEG	mCherry	×	×	97
	AD-PEI, CD-PEI, mHph3 and iRG conjugated DOTAP liposomes	Plk1	Tumor	I.V.	98
	Carboxylated branched PBAE	ReNL reporter	Orthotopic glioma tumors	I.C.	99
	PEI, lecitin, cholesterol, DOGS-NTA(Ni)	DPP-4	Liver	I.V.	100
	Boronic acid–rich dendrimer	EGFP, AAVS1, HBB, and CTNNB1	×	×	101
	PLys100-CA-mPEG77	RUNX1, STAT3	Tumor	I.V.	102
	NTA-SS-PEG-PCL, iRGD-PEG-pAsp(DAB)	Nrf2	Tumor	I.V.	103
	AD-disulfide-guanidyl, β-CD-PEI, HA	mutant KRAS	Tumor and lung	I.V.	104

	Polymethacrylates (combinatorial library)	mCherry reporter	×	×	105
	PEI, lecithin, cholesterol, DOGS-NTA(Ni), anti-EGFR, DPPE	KRAS	Tumor	I.V.	106
	AD and β-CD conjugated PBAP	mCherry	×	×	96
	PBAE, HPAE-EB	COL7A1	×	×	107
Lipidic delivery systems	Bioreducible lipids/cholesterol/DOPE/C16-PEG2K-ceramide (weight ratio 16/4/1/1)	GFP	×	×	108
	Bioreducible lipids/cholesterol/DOPE/DSPE-PEG2K (weight ratio 16/4/1/1)	IL1RAP	×	×	109
	Stemfect RNA transfection reagent	GFP	Tumor	I.T.	110
	NTA-lipidoid, cholesterol, DOPE, DSPE-PEG2K	GFP	×	×	111
	Lecithin, cholesterol, DOGS-NTA(Ni), DCP, DSPE-PEG-PDP, DPPE, DPPC	SRD5A2	Dermal papilla cells in the hair follicle	Topically on the depilated dorsal skin	112
	A fluorescent surfactant incorporated lipofectamine	GFP	×	×	113
	RNAiMAX	EGFP, EMX	Inner ear	Injected into mouse cochlea	114
	Bioreducible lipidoids/cholesterol/DOPE/DSPE-PEG2K (weight ratio 16/4/1/1)	GFP	Liver	I.V.	115
	5A2-SC8/cholesterol/zwitterionic lipids/DMG-PEG2K/permanently cationic lipids	Multiple genes	Muscle, brain, liver, lung	I.M., I.V., intrabrain	116
	DOTAP/cholesterol/DOPE/verteporfin (molar ratio of 1/1/0.94/0.06)	EGFP	In zebrafish model	Microinjection	117
Inorganic and inorganic/ organic hybrid delivery systems	CuS, PEI	Hsp90α	Tumor	I.T.	118
	Arginine-modified Au nanoassemblies	PTEN	Spleen, liver (macrophages)	I.V.	119
	ZIF-8	GFP	×	×	120
	Graphene oxide, PEG-PEI	EGFP	×	×	121
	AD-M12L24 MOC and β-CD-PEI	GFP	×	×	122
	RNP corona-Au nanoparticles	GFP	×	×	123
	Arginine-modified Au nanoassemblies	AAVS1, PTEN	×	×	124

	Black phosphorus nanosheets	Target 1, Grin2b, EGFP	Tumor	I.T.	125
	TAT-modified Au nanoclusters, DOTAP, cholesterol, DOPE, Gal–PEG–DSPE	Pcsk9	Liver	I.V.	126
	ZIF-90	GFP	×	×	127
	Cancer cell membrane coated ZIFs	EGFP	×	×	128
	US-powered Au Nanowires	GFP	×	×	129
	Au Nanoclusters	E6	×	×	130
	MSN, DOTAP, cholesterol, DOPE, DSPE-PEG2K	tdTomato	Brain	Intrastriatal injection	54
	Au nanoparticles, PEI, PEG	CCR5, γ-globin	×	Ex vivo	131
	Amine-functionalized mesoporous silica nanoparticles	GFP	×	×	132
	UCNP@SiO2, PEI	Plk1	Tumor	I.T.	133
	Mesoporous silica nanoparticle, DOTAP, cholesterol, DOPE, DSPE-PEG2K	Pcsk9, Apoc3, and Angptl3	Liver	I.V.	134
	Bi-functionalized aminoguanidine-PEGylated mesoporous organosilica	GFP	×	×	135
	TAT and aptamer modified Au nanorods	Plk1	×	×	136
	Au nanoparticles, pAsp(DET), thiol-DNA	HDR: DMD	Muscle	I.M.	137
	N–Zn-doped carbon dots	GFP	×	×	55
	Au nanorods, PEI, p-AZO, PEG	Hsp90α	Tumor	I.V.	138
	Silica NPs, PEG, GalNac-PEG	EGFP, Ai14 reporter, HDR: BFP to GFP	Retina, liver	Subretinal injection, I.V.	139
	PepFect14	EGFP reporter	×	×	140

Peptidic delivery systems	R9 peptide	EGFP, CCR5, ABCC11, EMX1, AAVS1	×	×	141
	Supramolecular amphiphilic peptide	EGFP	×	×	142
	R7L10 peptide	Bace1	Post-mitotic neurons of the brain	Intrabrain	143
	Genetic fusion of a supercharged polypeptide	CCR5	×	×	144
	Genetic fusion of a supercharged polypeptide	CCR5, AAVS1-AS2	×	×	145
	Genetic fusion of a low-molecular-weight protamine	KRAS	Tumor	I.T.	146
	dNP2 lipopeptide (HypaCas9)	EGFP	×	×	147
	Shuttle peptide	LoxP site	Lungs (mouse airway epithelia)	Intranasal injection	148
	Tandem peptide-lipid	GFP reporter	×	×	149
	Lipid-containing oligoaminoamides	EGFP	×	×	150
Bio-derived vesicles	Fusogenic glycoprotein decorated vesicles	EGFP	Heart	I.M.	151
	Nanomembrane-derived extracellular vesicles	DMD	Skeletal muscle	I.M.	152
	Pseudotyped lentivirus-like particles	B2M, TRAC	×	×	153
	Engineered murine leukemia virus-like particles	Hpd	HiPSC, HHSC, bone-marrow cells, mouse embryos, liver	Retro-orbital injection	154
	Gesicles	HIV LTR	×	×	155
	Extracellular vesicles	DMD exon 53	Muscle	I.M.	156
	Tetrahedral DNA nanostructure-extracellular vesicles	WNT10B	Tumor	I.V.	157
	Engineered exosomes	Stop-DsRed reporter	×	×	158

DNA-based delivery systems	DNA-g-PCL, DNA linker	GFP	×	×	159
	DNA nanoclew, PEI	GFP	Tumor	I.T.	160
	DNA nanoflower containing MUC1 aptamers and miR-21 binding sequence	EGFP	Tumor	I.T.	161
	Branched DNA structure	Plk1	Tumor	I.V.	162
Other delivery systems	Cas9 conjugate with asialoglycoprotein receptor ligands (ASGPrL)	EMX1	×	×	163
	Folate-targeted CDEH	Plk1	Tumor	I.T.	164
	Chitosan-coated RFP, RNP, ssDNA	HDR: BFP to GFP; knock-out: PRDX4	×	×	165
	Tetralysine modified H-chain apoferritin (TL-HFn)	GFP	Tumor	I.V.	166
	Protein-scaffolded CRISPR–Cas9 nanoassembly	EGFP, CD71	×	×	167

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