REVIEW

The reversed intra- and extracellular pH in tumors as a unified strategy to chemotherapeutic delivery using targeted nanocarriers

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Table S1 Inhibitors of proton transporters in cancer. In this table we summarize the inhibitors of proton transporters mentioned in the text. Although none of these compounds have reached clinical relevance, they have shown inhibitory activity on tumoral cells and mouse xenografts, improving in some instances the antitumoral activity of some known anticancer drugs.

Inhibitor name	Co-drug	Nanocarrier	*In vitro*/*in vivo* study	Ref.
V-ATPase inhibitors				
Omeprazole/lansoprazole	Doxorubicin	PEGylated liposomes	4T1 breast cancer cells	33
Lansoprazole	Paclitaxel	PLGA-NPs	MCF7 breast cancer cells	37
NHE inhibitors				
Cariporide	Mephalan	n/a	HUH-28 cholangiocarcinoma, MDA-MB231 & MCF7 breast cancer cells	21
MCT inhibitors				
CHCA	n/a	Liposomes	MCF7 & U-87MG glioblastoma cells	44
AZD3965	n/a	PEG-*b*-PDPA-NPs	TC1 mouse lung cancer cells / TC1 & B16F10 melanoma xenografts	48
CA inhibitors				
CL 5343	Maytansinoid	CL 5343-myatansinoid conjugates	SKRC52 kidney cancer cells & xenografts	53
Acetazolamide	Monomethyl-auristatin E	Acetazolamide-monomethyl auristatin E conjugates	Mice bearing SKRC52 xenografts	54
Fluoro-benzosulfonamide (CAL)	Tubulysin B	CAL-tubulysin B conjugates	HT29 colon cancer, SKRC52 & A549 lung cancer cells / HT29 & A549 tumor xenografts	55
Polyamino-polycarboxylamido aromatic sulfonamide	Tubulysin B	CA9 inhibitor-tubulysin B conjugates	HT29 tumor xenografts	57
VD11-4-2	Doxorubicin	Porous silicon NPs	MCF7 breast cancer cells	59
CA inhibitors				

Small molecular weight CA inhibitors designed by the authors	Doxorubicin	PEGylated gold NPs	HT29 tumor cells	60
Acetazolamide	CFM 4.16 + sorafenib	TPGS and SMA micellar nano formulation	A498 kidney cancer cells & xenografts	61
Acetazolamide	CDF or paclitaxel	Albumin-NPs	MDA-MB231 & MDA-MB468 breast cancer cells / breast cancer patient xenografts	52,62
Acetazolamide and sulfonamide 3a	n/a	Gold-NPs	n/a	63,64
Sulfonamide derivatives	n/a	Plasmonic-gold nanorods	HCT116 colon carcinoma & MDA-MB231 cells	65

PEG, poly(ethylene glycol); NPs, nanoparticles; PLGA, poly(lactic-*co*-glycolic acid); CHCA, *α*-cyano-4-hydroxycinnamic acid; PDPA, poly(dipropylaminoethyl methacrylate; CL 5343, 5-amino-1,3,4-thiadiazole-2-sulfonamide; TPGS, vitamin-E-*α*-D-tocopherol; SMA, styrene maleic anhydride; CDF, 3,4-difluorobenzyliden curcumin. n/a, not applicable.

Table S2 Main strategies to achieve a pH_e-induced drug release. Structural destabilization of nanocarriers.

pH_e-sensitive block/D-pH_e	Nanocarrier	Composition of nanocarrier	Drug delivered	*In vitro*/*in vivo* study	Ref.
Poly(histidine)/6.8	Polymeric micelles	Poly(L-histidine)-*b*-PEG & PLA-*b*-PEG	Adriamycin	n/a	73,74
	Polymeric micelles	Poly(L-histidine)-*b*-PEG & PLA-b-PEG	Doxorubicin	MCF-7 breast cancer cells xenografts in mice	75
	"Flower like" polymeric micelles	PLA-*b*-PEG-*b*-poly(L-histidine)	Doxorubicin	MCF-7 cells	76
	Polymersomes	Methoxy-PEG-*b*-(poly-L-histidine)$_2$	5(6)-FAM	n/a	77
	Hybrid polymeric vesicles	PEG methyl ether acrylate & Poly(L-lysine) & Poly(L-histidine)	Doxorubicin	CT26 murine cancer cells	78
	Nanoparticles	Dextran-*b*-poly(L-histidine) copolymer	Doxorubicin	HuCC-T1 cholangiocarcinoma cells	79
Poly(aspartic acid-*g*-imidazole)/6.5	Polymeric micelles	Poly(aspartic acid-*g*-imidazole)-*block*-PEG copolymer	Doxorubicin	Mice bearing subcutaneous MCF-7 cells tumors	80,81
Poly(beta-aminoester)/6.8 (PAE)	Polymeric micelles	Methyl ether PEG-poly(beta-amino ester)	Doxorubicin	Mice bearing subcutaneous B16F10 tumors	82
	Polymeric micelles	Methyl ether PEG-poly(beta-amino ester)	Camptothecin TRITC	Mice bearing MDA-MB231 tumors	83
Diethylaminopropyl/6.8 (DEAP)	Y-shape "worm-like" polymeric micelles	Methoxy-PEG block & two poly(L-lysine)-DEAP blocks	Chlorin e6 (Ce6)	Nude mice bearing KB tumors	84
mPEG-*b*-PCLL/6.8	Polymeric micelles	mPEG-*b*-PCLL	Doxorubicin	Mice bearing H22 hepatoma cells	85

D-pH_e, destabilization pH_e; PEG, poly(ethylene glycol); PLA, poly(L-lactic acid); 5(6)-FAM, 5(6)-carboxyfluorescein; TRITC, tetramethylrhodamine isothiocyanate; DEAP, diethylaminopropyl; mPEG-*b*-PCLL, methoxy PEG-*block*-poly(*N*(ϵ)-((1-carboxy-*cis*-cyclohexene)-2-carbonyl)-L-lysine). n/a, not applicable.

Table S3 Main strategies to achieve a pH_e-induced drug release. Gate opening in the nanocarriers.

pH_e-sensitive "gatekeeper"	Nanocarrier	Composition of nanocarrier	Drug delivered	*In vitro*/*in vivo* study	Ref.
Poly(histidine)	Nanoparticles	Mesoporous silica	Doxorubicin	n/a	86
Poly(2-pentamethylenimino) ethyl methacrylate (PPEMA)	PEGylated	Mesoporous silica nanoparticles	Doxorubicin	HeLa cells	87
Chitosan crosslinked with *N*,*N*'-bis(acryloyl)cystamine (BAC)	Nanoparticles	Mesoporous silica	Doxorubicin	HepG-2 cells	88

PEG, poly(ethylene glycol). n/a, not applicable.

Table S4. Main strategies to achieve a pH_e-induced drug release. Labile linkers at pH_e.

Labile linker at pH_e	Nanocarrier	Composition of nanocarrier	Drug delivered	*In vitro*/*in vivo* study	Ref.
2,3-Dimethylmaleic anhydride (DMMA)	Nanoparticles	PLA-*b*-PAEMA/DMMA block copolymers	Doxorubicin	HeLa cells	95
	Carbon dots	PEG-PAH//DMMA & carbon dots complex	Cisplatin (IV) prodrug	Mice bearing subcutaneous cervix U14 xenografts	96

PLA, poly(L-lactic acid); PAEMA, poly(2-aminoethyl methacrylate); PEG, poly(ethylene glycol); PAH, poly(allyamine hydrochloride).

Table S5 Main strategies to achieve a pH_e-induced internalization of nanocarriers. Surface charge modification.

pH_e-sensitive compound for the charge modification	Nanocarrier	Composition of nanocarrier	Drug delivered	*In vitro*/*in vivo* study	Ref.
Polysulfadimethoxine (PSDM)	Polymeric micelles	Poly(L-histidine)/PEI & α-methoxy ω-hydroxy-PEG-*b*-PSDM	Paclitaxel	Mice MCF-7 model	97
Poly(histidine)	Hybrid nanoparticles	Poly(L-histidine) core / PEGylated lipid shell	Doxorubicin	4T1 tumor-bearing mice	98
2,3-Dimethylmaleic anhydride (DMMA)	Nanogel	Poly(2-aminoethyl methacrylate hydrochloride) (PAMA)/DMMA	Doxorubicin	MDA-MB-435s tumor-bearing mice	99
	Polymeric micelles	Octadecyl-*g*-poly(2-hydroxyethyl aspartamide)/DMMA	Doxorubicin	MB-435 cells	100
	Hybrid micelles	Poly(lysine-*co*-*N*,*N*-bis(acryloyl) cystamine-*co*-DMMA	Doxorubicin	HeLa cells	102
Citraconic anhydride (derivative of DMMA)	Polymeric micelles	PASP-*g*-PEG-DDA-(hydrazone-DOX)-(ethylene-diamine-citraconic amide) conjugates	Doxorubicin	HepG2 cells	101

PEI, polyethyleneimine; PSDM, Polysulfadimethoxine; PEG, poly(ethylene glycol); DMMA, 2,3-dimethylmaleic anhydride; PASP, poly(aspartate); DDA, dodecylamine; DOX, doxorubicin.

Table S6 Main strategies to achieve a pH_e-induced internalization of nanocarriers and pH-mediated ligands activation.

pH_e-sensitive structure for the ligand activation	Nanocarrier	Composition of nanocarrier	Drug delivered/active targeting moiety	*In vitro*/*in vivo* study	Ref.
PEG chains attached by benzoic-imine bonds	PEGylated polymeric micelles	*α*-*β* Cyclodextrin dimer & Modified NIPAAm-*co*-NAS	Doxorubicin/RGD peptide	HeLa cells	103
PLGVR/PASP conjugate	Silica nanoparticles	Silica NPs functionalized with *β*-CD/RGD/PLGVR/PASP	Doxorubicin/RGD	SCC-7 & HT-29 cells	104
Poly(histidine)	Nanoparticles	TPGS-poly(histidine)-folate triblock copolymer & mPEG-PLA diblock copolymer	Docetaxel/folate	4T1 breast cancer cells	105

NIPAAm, *N*-isopropylacrylamide; NAS, *N*-acroyloxysuccinimide; RGD, Arg-Gly-Asp; PASP, poly(aspartic acid); PLGVR, Pro-Leu-Gly-Val-Arg

TPGS, D-*α*-tocopheryl polyethylene glycol succionate; mPEG-PLA, methoxypoly(ethylene glycol)-poly(D,L-lactic acid).

Table S7 Main strategies to achieve a pH_e-induced internalization of nanocarriers. pH-mediated PEG detachment.

pH_e-Sensitive block	Nanocarrier	Composition of nanocarrier	Drug delivered	*In vitro*/*in vivo* study	Ref.
PPC-DMMA	Nanoparticles	Thiolated polyethyleneimine with coating of PPC-DMMA	Poly like kinase 1 siRNA	Mice with MDA-MB-231 xenografts	106
PPC-DMMA	Nanoparticles	*β*-Cyclodextrin & PEI with coating of PPC-DMMA	miR34a	Mice bearing B16F10 xenografts	107

mPEG, methoxy poly(ethylene glycol); PAEP, poly(2-(2-aminoethoxy)ethoxy)phosphazene; PPC, $mPEG_{45}$-*b*-$PAEP_{75}$-cysteamine; DMMA, 2,3-dimethylmaleic anhydride; PEI, polyethylenimine.