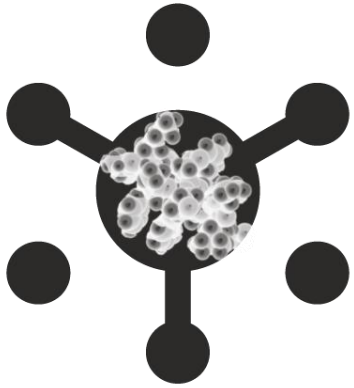

Metallomic Scientific Network No. 11440027

Application of Nanoparticles in Therapy and Imaging of Melanoma

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Date: 19-08-15

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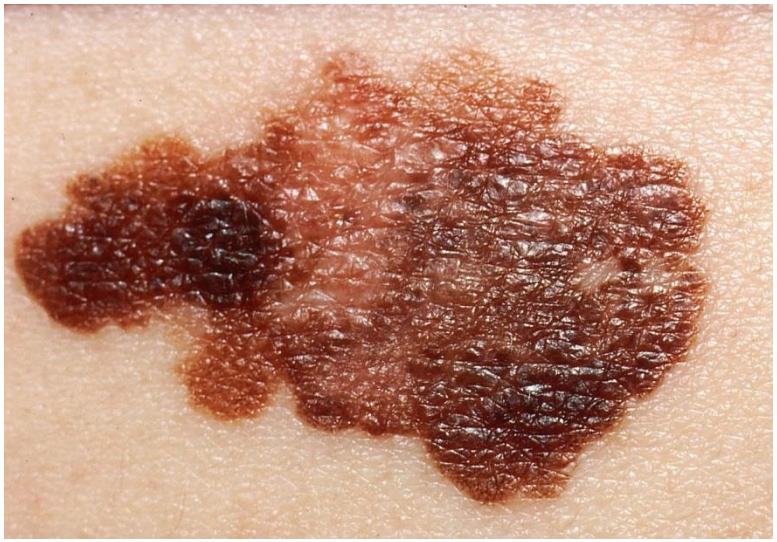
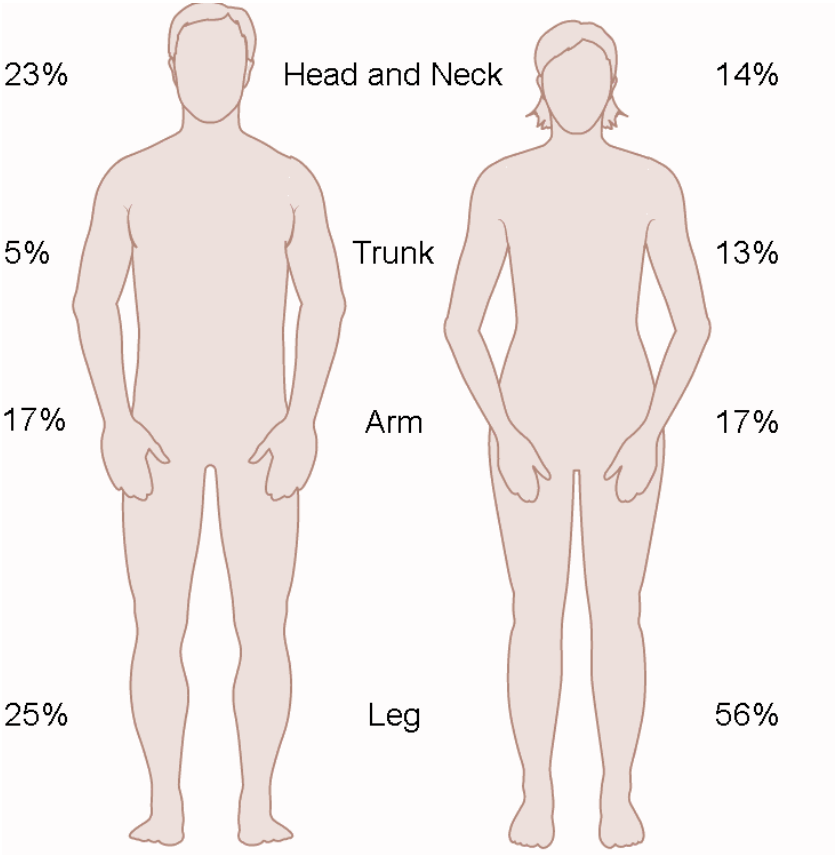
Melanoma

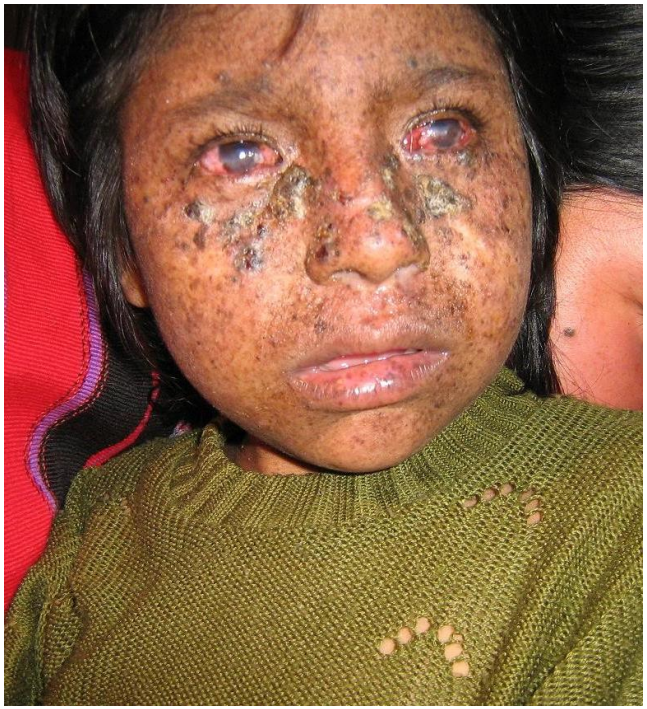


A melanoma of approximately 2.5 cm by 1.5 cm

Where melanoma is most likely to develop



Melanoma, also known as **malignant melanoma**, is a type of cancer that develops from the pigment-containing cells known as melanocytes. Typically they occur in the skin but may rarely occur in the mouth, intestines, or eye.



In women they most commonly occur on the legs, while in men they are most common on the back. Sometimes they develop from a mole with concerning changes including an increase in size, irregular edges, change in color, itchiness, or skin breakdown.

The primary cause of melanoma is ultraviolet light (UV) exposure in those with low levels of skin pigment. The UV light may be from either the sun or from tanning devices. About 25% develop from moles. Those with many moles, a history of affected family members, and who have poor immune function are at greater risk. A number of rare genetic defects such as **xeroderma pigmentosum** also increase risk. Diagnosis is by biopsy of any concerning skin lesion.

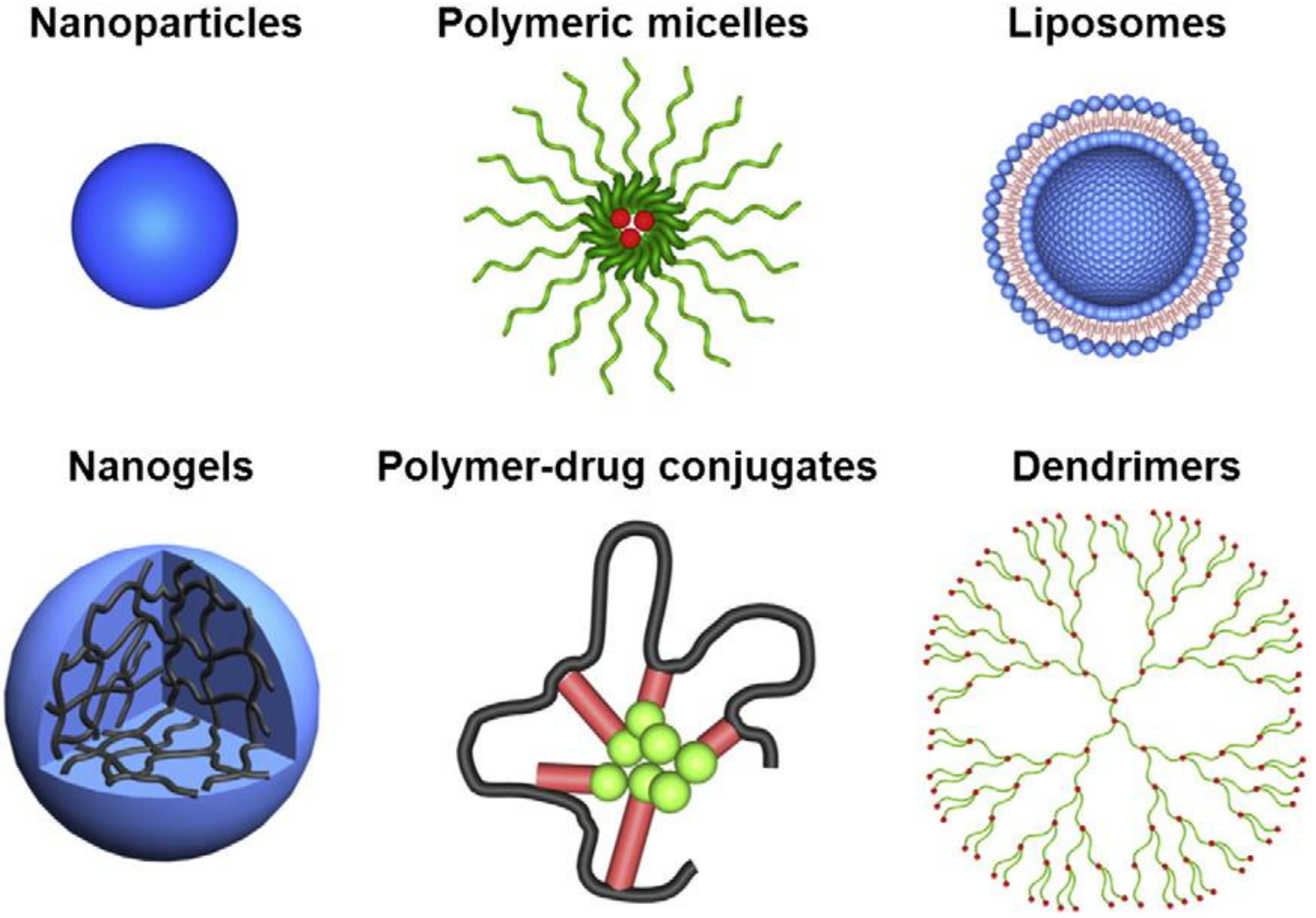
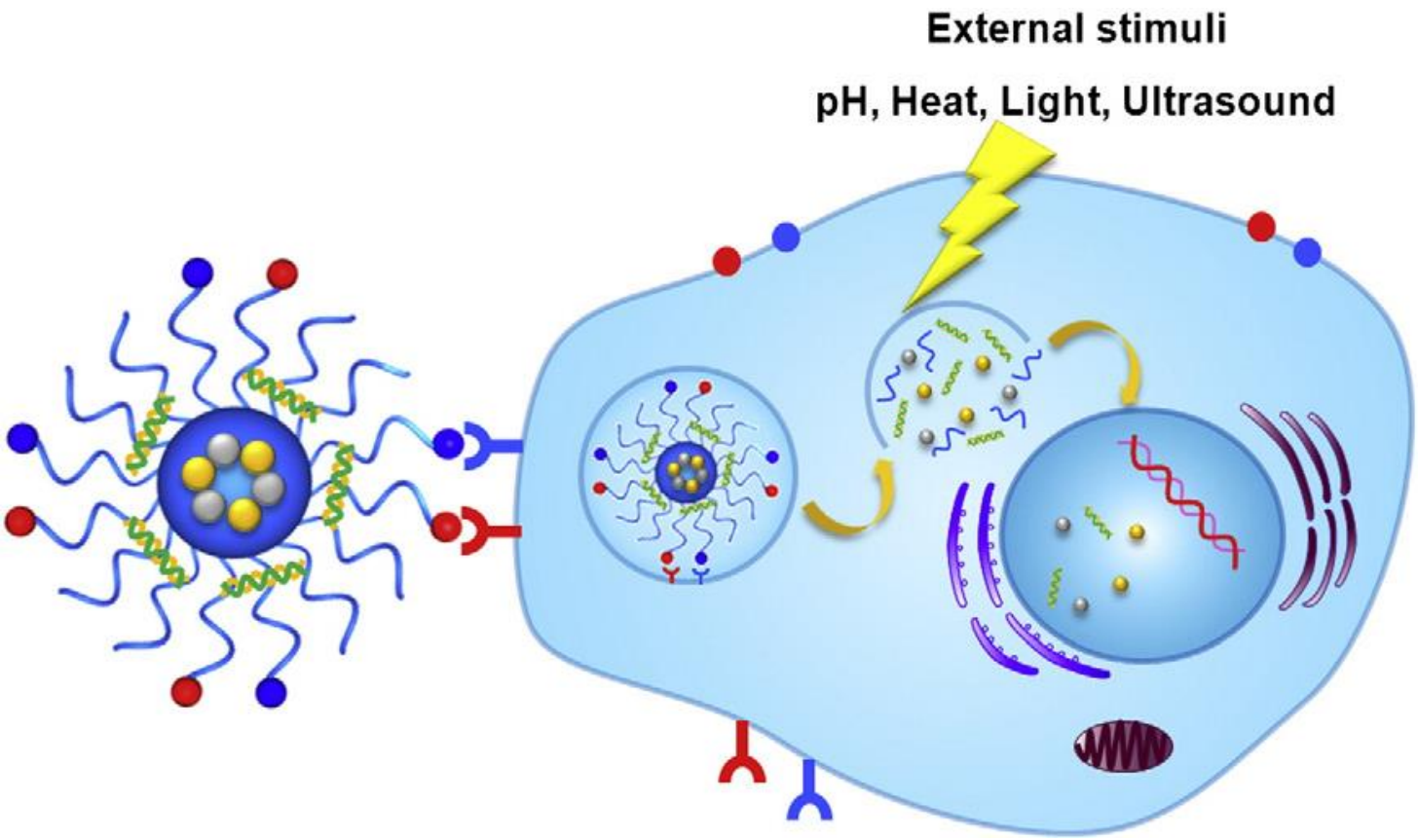
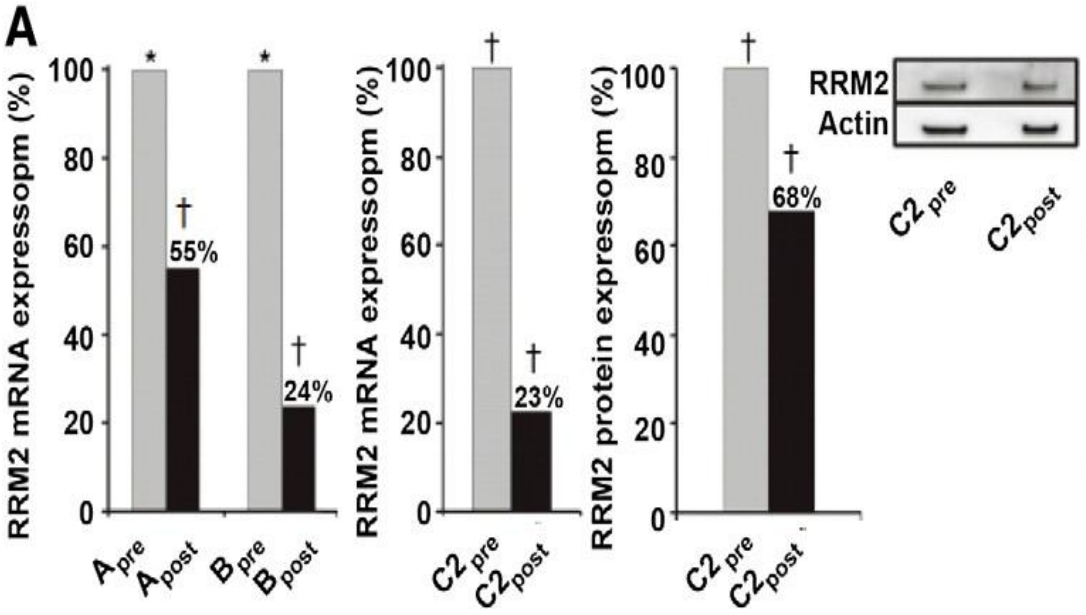


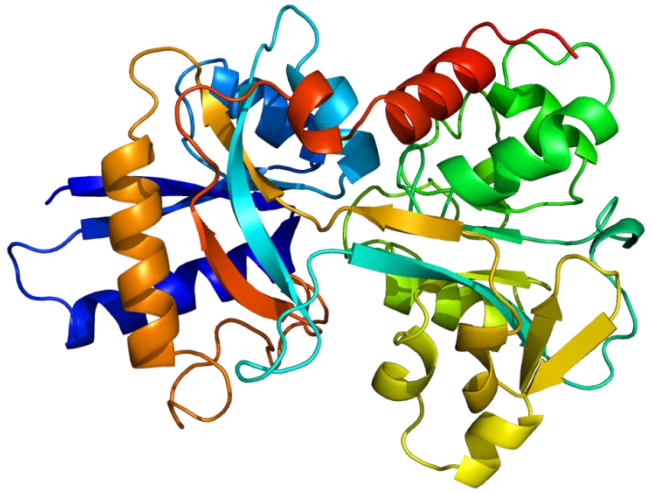
Illustration of the classification of various nanocarriers for drug delivery and release



Schematic illustration of the stimuli-triggered drug release from the NPs

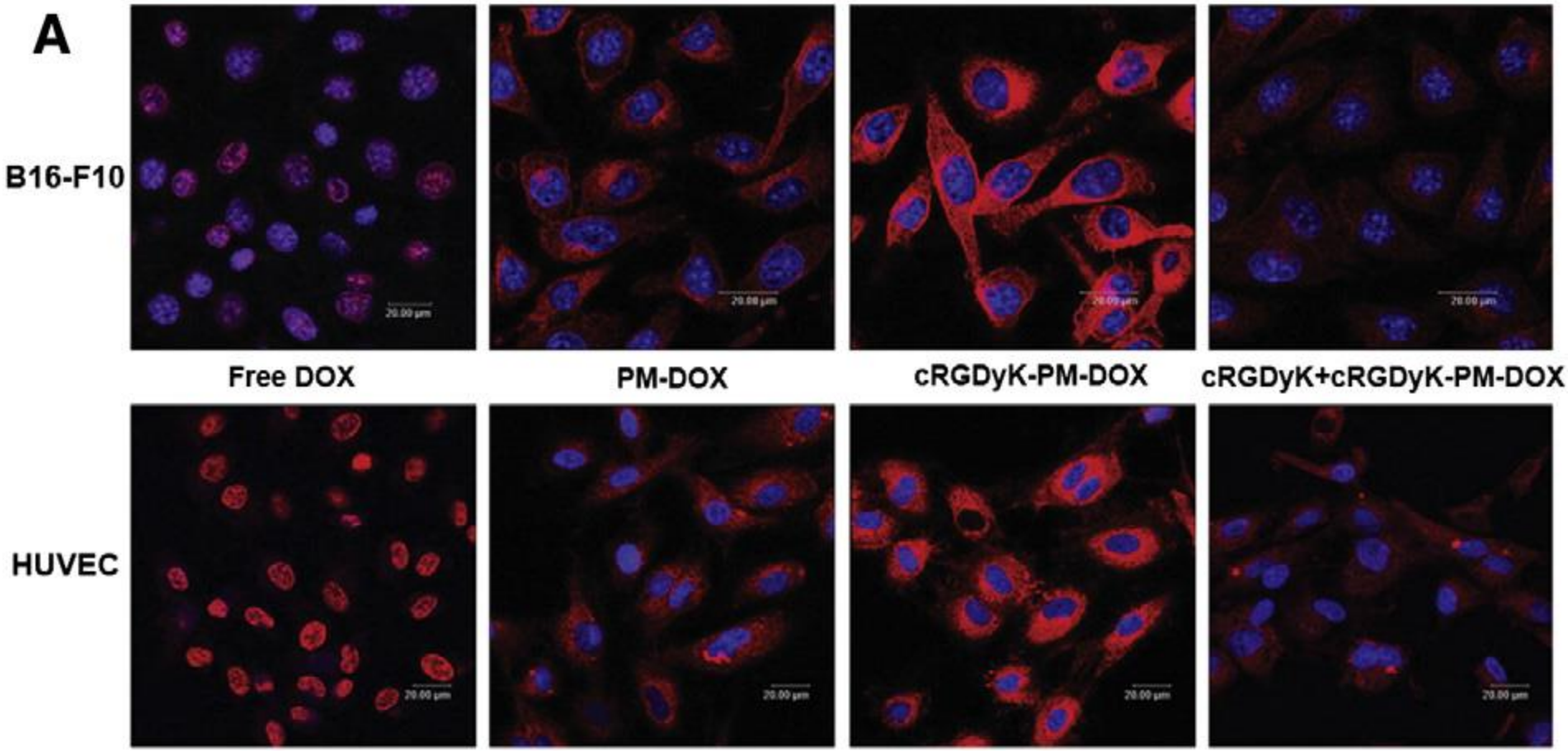
Transferrin conjugated nanocarriers for gene delivery to melanoma. (A) RRM2 mRNA and protein expression in samples from malignant melanoma patients A, B and C2 before and after dosing





Transferrin

Ribonucleotide reductase (RNR, also known as **ribonucleoside diphosphate reductase**) is an enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides. Deoxyribonucleotides in turn are used in the synthesis of DNA.



cRGDfK peptide conjugated NPs for drug delivery to melanoma (B16-F10) and vasculature endothelial cells (HUVEC). (A) Confocal laser scanning microscopy (CLSM) images of B16-F10 and HUVECs. Red signal represents fluorescence of DOX while blue signal represents nuclear fluorescence of Hoechst 33258. (B) Effect of various treatments on the apoptosis of tumor cells from B16-F10 melanoma mice model. antivascular agent combretastatin A4 (CA4), polymersic michelle(PM)

Specifically targeting melanoma cells/melanoma vasculature associated endothelial cells/dendritic cells through ligand–receptor mediated interactions

Specific ligand–receptor interactions	Therapeutic agents	Nanocarriers	Effect
Targeting melanoma cells			
Tf/TfR	siRNA of RRM2 subunit	Transferrin-bearing pegylated cyclodextrin-based polymer (CALAA-01)	Specific RRM2 gene expression inhibition and tumor growth suppression
	P73 plasmid DNA	Transferrin-bearing polypropylenimine dendrimer	Enhanced anti-proliferative activity and tumor growth inhibition
Folate/FR	IL-2 plasmid DNA	Polyethylenimine linked by beta-cyclodextrin and conjugated with folate (named H1)	Tumor growth suppression and prolonged survival
tbFGF/FGFR	DOX and PTX	tbFGF-LPs	Significant inhibition in tumor growth and improvement in survival rate
	PTX	tbFGF-PEG-LPs	Higher drug accumulation in tumor tissues and prolonged drug half-life time
Oct/SSTR	DOX	Oct–PEG–PE	Remarkable accumulation of DOX in melanoma tumors and the pancreas and more significant cytotoxicity to melanoma cells
YIGSR/laminin receptor	5-FU	YIGSR-SN	Significant efficacy in the prevention of tumor growth and lung metastasis
	Etoposide	YIGSR peptide conjugated micelles	Higher cytotoxicity to melanoma cells and a markedly inhibition in lung metastasis
AA/sigma receptor	MDM2, c-myc, and VEGF siRNA	LCP NP grafted with PEG and AA	Efficient tumor growth inhibition and metastasis suppression
	c-Myc siRNA	AA-targeted NPs	Partially inhibited tumor growth
MC1SP-peptide/ MCR-1	HSVtk	PEI-PEG-based polyplexes containing MC1SP-peptide	Efficient melanoma growth inhibition and prolonged the lifespan
Targeting melanoma vasculature associated endothelial cells			
RGD-base peptide/ αvβ3 integrin	DOX and CA4	RFPMs modified with PEG-PLA	Anti-tumor vasculature and anti-proliferation effect
cRGDfK peptide/αvβ3 integrin	PTX and CA4	cRGDfK peptide conjugated with PLGA modified solid NPs	Anti-tumor vasculature and anti-proliferation effect

Abbreviations: Tf, transferrin; TfR, transferrin receptor; FR, folate receptor; tbFGF, truncated human basic fibroblast growth factor; FGFR, fibroblast growth factor receptor; tbFGF-LPs, tbFGF-modified liposomes; DOX, doxorubicin; PTX, paclitaxel; tbFGF-PEG-LPs, tbFGF-modified PEGylated liposomes; Oct, octreotide; SSTR, somatostatin receptor; Oct–PEG–PE, octreotide–polyethylene glycol–phosphatidylethanolamine; YIGSR, Tyr–Ile–Gly–Ser–Arg; YIGSR-SN, YIGSR peptide anchored pegylated nanospheres; RRM2, ribonucleotide reductase M2 subunit; 5-FU, 5-fluorouracil; AA, anisamide; LCP NP, Lipid/calcium/phosphate nanoparticle; MCR-1, melanocortin receptor-1; HSVtk, herpes simplex virus thymidine kinase suicide gene; RGD, arginine–glycine–aspartic acid; CA4, combretastatin A4; RFPMs, RGD functionalized polymeric micelles; Ac-PHSCN-NH(2), *N*-acetyl-proline-histidine-serine-cysteine-asparagine-amide; C16Y-L, C16Y peptide-modified liposomes; Anx, galectin-1-specific anginex; Anx/RGD-L, Anx and RGD dual-conjugated liposomes; TH10, 10 peptides with sequence of TAASGVRSMH; CTL, cytotoxic T lymphocyte; MART-1, melanoma antigen recognized by T-cells 1; Man(11)-LPR100, mannosylated and histidylated lipopolyplexes; SPION, superparamagnetic iron oxide nanoparticle; DC-SIGN, DC-specific intercellular adhesion molecule-3-grabbing nonintergrin.

Specifically targeting melanoma cells/melanoma vasculature associated endothelial cells/dendritic cells through ligand–receptor mediated interactions

Specific ligand–receptor interactions	Therapeutic agents	Nanocarriers	Effect
Ac-PHSCN-NH(2)/ α5β1 integrin	DOX	Ac-PHSCNK-NH(2) (PHSCNK) conjugated with stealth liposomes	Enhanced intracellular uptake and much stronger tumor inhibition
C16Y peptide/αvβ3 andα5β1 integrin		C16Y-L	Higher intracellular uptake and enhanced antitumor effect
Anx and RGD/galectin-1 andαvβ3 integrin		Anx/RGD-L	Significantly enhanced synergistic targeting effect and specificity on the tumor vasculature than single target
TH10 peptide/NG2	DTX	TH10-DTX-NPs	Pericyte apoptosis with decreased microvessel density in lung metastasis and enhanced antitumor effect
Targeting dendritic cells			
DC-SIGN-binding glycans/DC-SIGN	MART-1	DC-SIGN-binding glycans modified liposomes	More efficient antigen presentation to T cells and drive CD8(+) T cells differentiation
CD11c and DEC-205 single chain antibody fragments/CD11c and DEC-205	OVA or OVA peptide antigen	CD11c and DEC-205 single chain antibody fragments conjugated stealth liposomes	Induction of dramatic B16-OVA-specific CTL responses, significant protection against tumor growth and prolonged melanoma-free survival
Mannose/mannose receptor	MART-1 mRNA	Man(11)-LPR100	Significant anti-melanoma immune responses and tumor growth inhibition
DC-SIGN antibody/ DC-SIGN	Fluorescently labeled antigen	SPION coated with antibodies recognizing DC-SIGN	Two imaging agents within a single carrier allows tracking of targeted nanovaccines on a subcellular, cellular and possibly organism level

Abbreviations: Tf, transferrin; TfR, transferrin receptor; FR, folate receptor; tbFGF, truncated human basic fibroblast growth factor; FGFR, fibroblast growth factor receptor; tbFGF-LPs, tbFGF-modified liposomes; DOX, doxorubicin; PTX, paclitaxel; tbFGF-PEG-LPs, tbFGF-modified PEGylated liposomes; Oct, octreotide; SSTR, somatostatin receptor; Oct–PEG–PE, octreotide–polyethylene glycol–phosphatidylethanolamine; YIGSR, Tyr–Ile–Gly–Ser–Arg; YIGSR-SN, YIGSR peptide anchored pegylated nanospheres; RRM2, ribonucleotide reductase M2 subunit; 5-FU, 5-fluorouracil; AA, anisamide; LCP NP, Lipid/calcium/phosphate nanoparticle; MCR-1, melanocortin receptor-1; HSVtk, herpes simplex virus thymidine kinase suicide gene; RGD, arginine–glycine–aspartic acid; CA4, combretastatin A4; RFPMs, RGD functionalized polymeric micelles; Ac-PHSCN-NH(2), *N*-acetyl-proline-histidine-serine-cysteine-asparagine-amide; C16Y-L, C16Y peptide-modified liposomes; Anx, galectin-1-specific anginex; Anx/RGD-L, Anx and RGD dual-conjugated liposomes; TH10, 10 peptides with sequence of TAASGVRSMH; CTL, cytotoxic T lymphocyte; MART-1, melanoma antigen recognized by T-cells 1; Man(11)-LPR100, mannosylated and histidylated lipopolyplexes; SPION, superparamagnetic iron oxide nanoparticle; DC-SIGN, DC-specific intercellular adhesion molecule-3-grabbing nonintergrin.

NPs mediated stimuli-responsive drug delivery to melanoma

Therapeutic agents	Nanocarriers	Effect
pH		
Gemcitabine	PEG and C18 (a hydrophobic stearic acid derivative) modified micelles	Gemcitabine in the acid-sensitive micelles was more cytotoxic than in the acid-insensitive micelles under acidic tumor microenvironment
DOX-MA	mPEG-b-p (HPMAm-Lac(n)) polymeric micelles	Higher cytotoxicity and better antitumor activity
5-FU	PEG-chitosan based nanogel	Enhanced antitumor effect but reduced toxicity
Cisplatin	PNIPAM modified AuNPs	Enhanced cytotoxicity against melanoma than free cisplatin
pGL3-promoter DNA	Carboxymethyl poly (L-histidine) coated poly (beta-amino ester)	Significant improvement in transfection efficiency
Temperature		
DOX	Stealth TSL	Improved tumor growth inhibition and enhanced survival
GA	FMP	Better antitumor effects
Light		
CdTe(710) QDs	QDs coated with a silica shell	Significant inhibition of melanoma growth after laser irradiation
HAuNS	NDP–MSH–PEG–HAuNS	Significant photo-thermal ablation of melanoma after laser irradiation
Dual-photosensitizers	Mesoporous-silica-coated upconversion fluorescent NPs	Convert NIR light to visible wavelengths and showed significant tumor growth inhibition
Ultrasound		
Melanoma antigen	Erfluoropropane gas-entrapping liposomes (Bubble liposomes)	Activate melanoma specific cytotoxic T lymphocytes and prevent the melanoma lung metastasis
Plasmid DNA of gp100 and TRP-2	Man-PEG(2000) bubble lipoplexes	Enhanced melanoma growth inhibition and metastatic prevention
DOX	Microbubbles	Elevated tumor cell killing efficiency

Abbreviations: DOX-MA, DOX methacrylamide derivative; TSL, thermosensitive liposome; GA, geldanamycin; PNIPAM, poly-*N*-isopropylacrylamide; FMP, thermosensitive ferromagnetic particle; HAuNS, hollow gold nanosphere; QD, quantum dot; NDP–MSH–PEG–HAuNS, HAuNS modified with PEG and alpha-melanocyte-stimulating hormone analog.

The applications of nanotheranostics in melanoma

Imaging agents	Therapeutic agents	Nanocarriers	Effect
Ag–Au bimetallic NP	Temozolomide	Nanogel consists of Ag–Au bimetallic NP core and PEG-based hydrogel shell	Strong visible fluorescence for melanoma imaging and thermo-triggered temozolomide release
QDs and MNPs	PTX	PTX–QDs–MNPs-loaded PLA NPs	Melanoma growth inhibition and melanoma imaging
Two different chromo-fluorogenic components		Polymeric NPs	Dual-color fluorescence imaging and bimodal phototherapeutic performance
MBCSP	Curcumin and DOX	MBCSP conjugated with GRGDS peptides	Tumor imaging under MRI and synergistical melanoma growth inhibition
QDs	Anti-CSE1L antibody	Anti-CSE1L antibody conjugated NPs	Both capabilities of melanoma imaging and metastasis suppression
	Cisplatin	QDs–liposomes	Melanoma imaging and higher cytotoxic activity

Abbreviation: GRGDS, Gly–Arg–Gly–Asp–Ser; MNP, magnetic nanoparticle; MBCSP, magnetic-based core–shell particle.

Li, J., Wang, Y., Liang, R., An, X., Wang, K., Shen, G., et al. (2015). Recent advances in targeted nanoparticles drug delivery to melanoma. *Nanomedicine: Nanotechnology, Biology and Medicine, 11*(3), 769-794

NPs for melanoma combination therapy

Combinational therapeutic agents	Nanocarrier	Effect
Chemotherapeutics combination therapy		
PTX and CA4	PLGA NPs conjugated with cRGDfK peptide	Dramatic tumor vasculature disruption and tumor growth inhibition
Imatinib and DOX	SSL	Significant tumor growth inhibition at a low dose
Chemotherapy with immunotherapy		
PTX and SP-LPS	Self-assembled NPs	Higher antitumor activity and a higher percentage of activated immune cells infiltration
PTX and Ad5-mIL-12	AL	Significant enhanced antitumor effect
Gene combination therapy		
$BRAF^{V600E}$ and AKT3 siRNA	Liposome	Cooperative tumor growth inhibition and metastasis suppression
Bcl-2/VEGF/c-Myc siRNA	ABP	Effective regression of advanced stage tumors
MDM2/c-Myc/VEGF siRNA	LCP NP, LPH	Efficient tumor growth inhibition with less systemic toxicity

Abbreviations: SP-LPS, soluble lipopolysaccharides; Ad5-mIL-12, adenovirus encoding for interleukin-12; AL, anionic liposome; SSL, sterically stabilized liposome; ABP, arginine-grafted bioreducible poly (disulfide amine) polymer; VEGF, vascular endothelial growth factor; LPH, liposome–polycation–hyaluronic acid.

Thank you for your attention

The project is supported by International Visegrad Fund, www.visegradfund.org

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