Chapter

19

CANCER TARGETING STRATEGIES OF NANOMATERIALS

Jeong-Hun Kang[1], Riki Toita[2], Takahito Kawano[3], and Masaharu Murata[3,4*]

[1] Division of Biopharmaceutics and Pharmacokinetics, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan
[2] Department of Biomaterials, Faculty of Dental Science, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
[3] Innovation Center for Medical Redox Navigation, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan
[4] Department of Advanced Medical Initiatives, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

*Corresponding author: m-murata@dem.med.kyushu-u.ac.jp

Contents

19.1. INTRODUCTION

Cancer (a malignant tumor) is the leading cause of disease-related death, and 8.2 million cancer-related deaths were reported by the World Health Organization in 2012 [1]. Among cancer types, the most common causes of cancer death are lung, liver, and stomach cancers [1,2]. Surgery, chemotherapy, immunotherapy, and radiotherapy, either alone or in combination, can be used to treat cancer [3-5]. In recent years, there has been increasing interest in targeted delivery of therapeutic molecules (*e.g.,* genes, drugs, or proteins), which has several advantages over other forms of treatment: (1) enhanced therapeutic efficacy, (2) avoidance of undesired side effects caused by the delivery of therapeutic molecules to normal (healthy) cells; and (3) reduction of the efficacious dose of therapeutic molecules [6,7].

Cancer-targeted delivery systems for therapeutic molecules can be grouped into three categories: viral nanomaterials (*e.g.*, inactivated retroviruses, adenoviruses, adeno-associated viruses, and herpes simplex viruses), non-viral nanomaterials (*e.g.,* synthetic polymers and liposomes), and bacterial carriers (*e.g.*, *Clostridium*, *Salmonella*, and *Bifidobacterium*). Viral nanomaterials show high transfection efficiency, but have clinical safety issues (*e.g.,* immune responses) that must be solved before their use in clinical trials. Furthermore, because viral nanomaterials themselves do not have the ability to target cancer cells, their conjugation to cancer-specific ligands or promoters are required for cancer targeting [8-10]. Non-viral nanomaterials have several advantages such as low pathogenicity and that they easily can be mass-produced, but their disadvantages are low transfection efficiency and low cancer targeting capabilities; thereby, also requiring the use of cancer-specific ligands [11,12]. Anaerobic bacteria are mainly used as bacterial carriers for the delivery of therapeutic molecules to hypoxic cancer cells. They have high transfection efficiency, but also cause clinical safety problems such as inflammation and immune responses [13].

In this chapter, we focus on cancer targeting methods using nanomaterials for cancer cell-targeted therapy.

19.2. CANCER-TARGETING METHODS

Cancer targeting by nanomaterials is accomplished by either passive or active targeting. In the case of active targeting, nanomaterials typically recognize or respond to overexpressed receptors, overexpressed intracellular signals, or hypoxic regions in cancer cells and tissues (Table 1).

Table 1. Advantages and disadvantages of cancer targeting methods for clinical applications [6]

Passive cancer targeting method, the enhanced permeability and retention effect (EPR)		Active cancer targeting method					
		Nanomaterials targeting overexpressed receptors in cancer cells		Nanomaterials targeting overexpressed cellular signals (proteases and protein kinases) in cancer cells		Nanomaterials targeting hypoxic cancer regions	
Advantages	Disadvantages	Advantages	Disadvantages	Advantages	Disadvantages	Advantages	Disadvantages
1. High specificity for solid cancers 2. Applicable to various types of drugs or nanomaterials 3. Reduced side effects	1. Low EPR effect in poorly vascularized regions 2. Low therapeutic value in spreading and metastatic cancers	1. High specificity for cancers 2. Reduced side effects 3. Enhanced therapeutic efficacy	1. Lack of ligands responding to overexpressed receptors 2. Different activity levels of receptors between patients	1. High specificity for cancers 2. Reduced side effects 3. Enhanced therapeutic efficacy	1. Lack of selective peptides or proteins responding to overexpressed cellular signals 2. Different activity levels of cellular signals between patients	1. High specificity for hypoxic cancers 2. Enhanced therapeutic efficacy	1. Lack of useful vectors 2. Clinical safety issues and risk of side effects

19.2.1. Passive cancer targeting method

Cancer cells require oxygen and nutrients to promote their growth and progress. Therefore, the formation of new blood vessels *via* angiogenesis is essential for cancer growth and metastasis. Cancer angiogenesis is trigged by multiple pro-angiogenic factors, including vascular endothelial growth factor (VEGF), angiopoietins, basic fibroblast growth factor (bFGF) and cytokines [interleukin-1 (IL-1), and tumor necrosis factor α (TNFα)]. In addition to chemoattractants, integrins ($\alpha_v\beta_3$ and $\alpha_5\beta_1$), receptors (VEGF receptors), and circulating bone marrow-derived cells (F4 / 80$^+$CD11b$^+$ macrophages and Gr1$^+$CD11b$^+$ neutrophils) directly and / or indirectly participate in the angiogenic process of cancer [14,15]. Blood vessels near cancer cells are often dilated, leaky, tortuous, and heterogeneous.

The passive cancer targeting method is based on the EPR effect that is characteristic of blood vessels near cancer cells. Therefore, when nanomaterials or anti-cancer drugs are injected into the blood stream, they accumulate in cancer cells through these dilated, leaky, tortuous, and heterogeneous blood vessels near cancer tissues when compared with normal tissues that have blood vessels showing a well-organized and functional structure (Figure 1) [16]. However, the vessel structure and pore size of blood vessels within individual cancer types is different [17]. Thus, EPR-based cancer therapy using nanoparticles can exhibit different therapeutic efficacies depending upon the cancer type. The synthesis of optimized nanomaterials for each target cancer type is essential for efficient EPR-based cancer therapy.

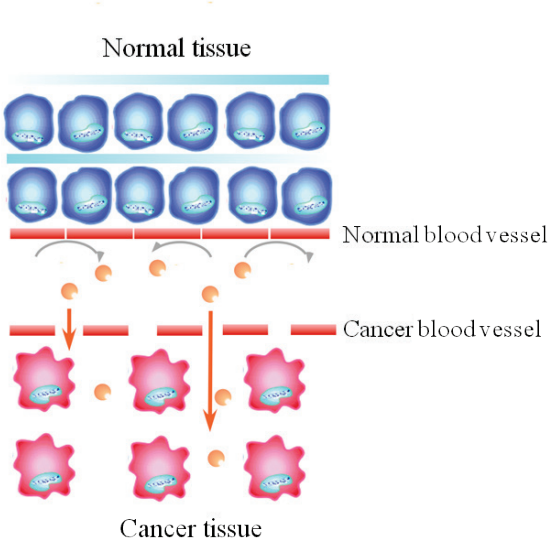

Figure 1. Schematic illustration of the EPR effect. Unlike normal blood vessels showing a well-organized and functional structure, cancer blood vessels are leaky, tortuous, and heterogeneous. Nanomaterials injected into the blood stream can pass through these cancer blood vessels and tend to accumulate in cancer tissues, but none or very few pass through normal blood vessels that have a well-organized and functional structure. Figure 1 has been reproduced from a previous publication [6].

19.2.1.1. Characteristics of nanomaterials that influence EPR

Several nanomaterial characteristics might affect the EPR effect, such as size [17-19], surface charge [17-19], hydrophobicity (high hydrophobicity increases the affinity for the cell membrane) [20], flexibility (high flexibility leads to rapid renal clearance) [18,19], and shape (spheres have a higher uptake by macrophages as compared with rods) [18,19]. Among these factors,

size and surface charge of nanomaterials may be the most important factors influencing the EPR effect.

19.2.1.1.1. Size of nanomaterials

Nanomaterials smaller than 5.5 nm mainly undergo kidney excretion and those larger than 8 nm are rapidly cleared through the reticuloendothelial system organs (liver and spleen) [18,21]. Normal blood vessels can permeate smaller nanomaterials (< 20 nm), but blood vessels near cancer cells are permeable to nanomaterials of < 400 nm in diameter [17,19,22]. Indeed, poly(ethylene glycol) (PEG)-liposomes of 400 nm in diameter can penetrate into the cancer interstitium, but those of 600 nm are excluded from extravascular spaces [22]. However, the most efficient EPR-based therapy might be obtained using nanomaterials between 10–200 nm in diameter [23]. A previous study reported that nanomaterials with a molecular weight (MW) greater than 40 kDa exhibited a high EPR effect [24]. However, other studies suggested that the EPR effect did not depend on the molecular weight (MW) of nanomaterials [22,25]. Therefore, the size of nanomaterials may be more important for efficient EPR than is the MW.

19.2.1.1.2. Charge of nanomaterials

Negatively charged nanomaterials are taken up rapidly by phagocytes (macrophages) and are degraded or discharged from the body. Nanomaterials with high positive charges can bind to blood proteins or to the surface of blood vessels, resulting in rapid kidney excretion and low accumulation in cancer cells [17,19]. The uptake of nanomaterials (150 nm) by macrophages was increased in the order of −40 > −25 > −15 mV negative surface charge and +35 > +25 > +15 mV positive surface charge [26]. Therefore, neutral or weakly positive-charged nanomaterials are more efficient for EPR compared with strong negatively-charged or positively-charged nanomaterials.

19.2.2. Active cancer targeting method

19.2.2.1. Overexpressed receptors in cancer cells

Cancer cells overexpress numerous receptors. The binding of ligands to overexpressed target receptors plays a key role in the growth, survival, metastasis, angiogenesis, and apoptosis of cancer cells (Figure 2). Examples of this are the binding of EGF and FGF to growth factor receptors (tyrosine kinase receptors) [27,28], and prostaglandin E and lysophosphatidic acid to G-protein-coupled receptors [29]. However, TNFα and TNF-related apoptosis inducing ligand (TRAIL) can stimulate apoptosis of cancer cells by binding to death receptors. However, death receptors and their downstream signals (*e.g.*, caspases) are often suppressed in cancer cells [30-32]. Therefore, nanomaterials recognizing overexpressed receptors in cancer cells might be useful for cancer-targeted therapy.

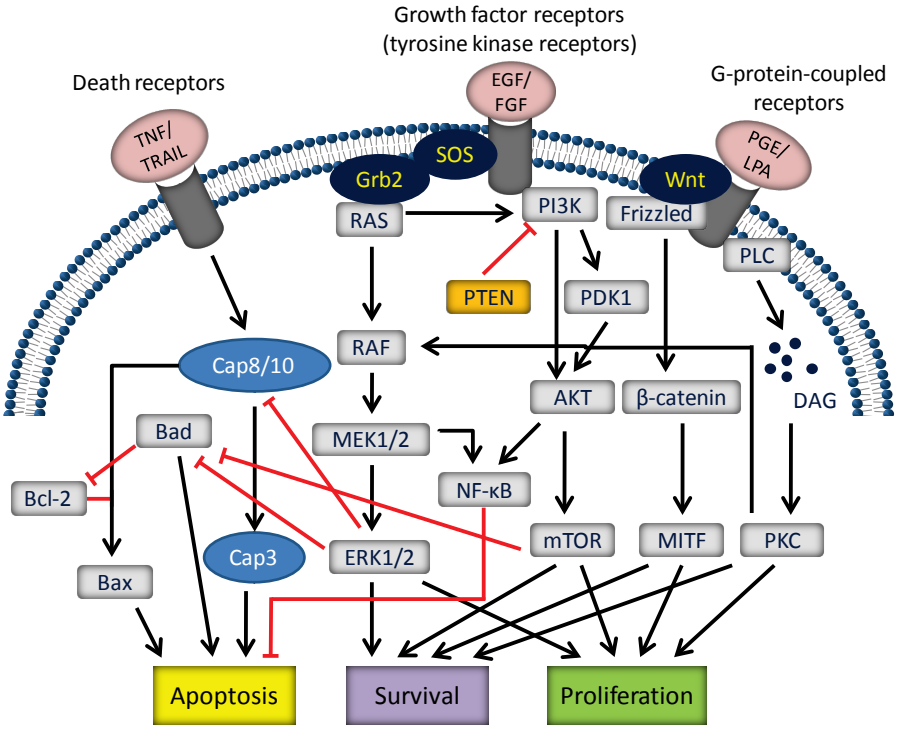

Figure 2. Signal transduction pathways are different in cancer cells compared with normal cells. Cancer cells overexpress receptors (growth factor receptors and G-protein-coupled receptors) and intracellular signaling molecules (ras/raf/mek/erk and pi3k/akt/mtor) that are related to cell survival and proliferation. However, apoptosis-related receptors (death receptors) and intracellular signals (caspases) are suppressed. Therefore, nanomaterials targeting or responding to overexpressed receptors or cellular signals of cancer cells can be useful for cancer cell-targeted therapy. Figure 2 has been modified from previous publications [59,92].

19.2.2.1.1. Nanomaterials targeting overexpressed receptors in cancer cells

Many receptor-specific ligands (aptamers, proteins, peptides, and antibodies) have been reported to be useful materials for targeting overexpressed receptors on cancer cells. Although transferrin and folate, which recognize transferrin receptor (TfR) and folate receptor, respectively, are extensively used to target various cancer cells, most nanomaterials containing receptor--specific ligands were identified by using limited numbers of cancer cells that overexpressed target receptors (Table 2). For instance, although targeting and therapeutic efficacy of folate-conjugated nanomaterials have been investigated using 9L / LacZ rat gliosarcoma cells [33], IGROV-1 human ovarian cancer cells [34], SKOV-3 human ovarian cancer cells [35], and B16 mouse melanoma cells

[36], the most commonly used cells are KB human epidermoid carcinoma and HeLa human epidermoid carcinoma cells, because they have an especially high overexpression of folate receptors [37-43]. It is important to note that receptor expression may vary according to the cancer cell type. For example, the antisense delivery efficiency of TfR-targeted, protamine-containing lipid nanomaterials was in the order of K562 > MV4-11 > Raji human leukemia cells, which was directly related to the TfR expression level. Thus, the higher the TfR expression, the greater the down-regulation of the target gene by nanomaterials [44].

Several receptor-specific peptides in Table 2 have been investigated, such as homing peptides identified from various library methods (the phage display peptide library method) (for review, see [45-47]). Nanomaterials containing these homing peptides can be used for cancer cell-targeted therapy. For example, the small heat shock protein 16.5-derived nanocage conjugated to a human hepatocellular carcinoma cell-specific peptide SP94 (SFSIIHTPILPL) was identified by an *in vivo* phase display method, and achieved selective targeting to HepG2 and HuH-7 human hepatocellular carcinoma cells, but not to HeLa cells or RLN-8 rat hepatocytes [48].

Double-targeted nanomaterials conjugated to dual-ligands, such as transferrin and folate [49], cyclic RGD (cRGD) and transferrin [50], glucose and folate [51], and RGD and IL-13 peptide (CGEMGWVRC) [52], have been developed to increase therapeutic efficacy against target cancer cells or to target specific cancer cells. Gold nanoparticles conjugated to folate and glucose showed a higher uptake by human epidermoid carcinoma (KB) cells than did gold nanomaterials conjugated to either folate or glucose alone [51]. Similarly, when transferrin and folate were linked to PEG-phosphatidylethanolamine, the transfection efficiency in HepG2 human hepatocellular carcinoma cells was higher for the conjugate than for the single ligand-modified nanomaterials [49]. Furthermore, nanomaterials linked with RGD and IL-3 peptide [52], and cRGD and transferrin [50] successfully targeted human umbilical vein endothelial and C6 rat glioma cells, and human umbilical vein endothelial and HeLa human epidermoid carcinoma cells, respectively.

In contrast, several studies have suggested that cancer-specific ligand-conjugated nanomaterials did not preferentially localize to cancer tissues in comparison with non-conjugated nanomaterials [53-55]. In these studies, despite the lack of change in cancer localization, ligand-conjugated nanomaterials showed enhanced uptake by cancer cells compared with non--conjugated nanomaterials, indicating that the increased therapeutic efficacy against cancer cells by ligand-conjugated nanomaterials was caused by increased uptake by cancer cells rather than by their localization to cancer cells [53-55].

19.2.2.2. Overexpressed cellular signals in cancer cells

Living cells contain numerous intracellular signal transduction pathways that play a key role in cell growth, differentiation, proliferation, and apoptosis. These signal pathways are tightly regulated and function normally in healthy cells. However, in cancer cells, many signal pathways related to cellular survival and proliferation are overexpressed, such as the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathway. In some cases, apoptosis-related signal pathways are suppressed, such as the death receptor-mediated pathways (Figure 2). Therefore, nanomaterials that could respond to these overexpressed intracellular signals could also be used for cancer-targeted therapy.

19.2.2.2.1. Nanomaterials targeting overexpressed cellular signals (proteases and protein kinases) in cancer cells

Cellular signal transduction pathways often are stimulated or suppressed through phosphorylation by protein kinases, or by dephosphorylation or cleavage by proteases. Phosphorylation reactions mediated by protein kinases add a phosphate group from adenosine triphosphate to the phosphorylation sites (serine, threonine, and tyrosine) [56,57] located on proteins. Nanomaterials that recognize overexpressed protein kinases are related to the phosphorylation reaction. Phosphorylation of nanomaterials containing target peptides can add two anionic charges of the phosphate to target peptide substrates, thereby weakening electrostatic interactions in the nanomaterials. For example, protein kinase C (PKC)α and protein kinase A (PKA) are overexpressed in several cancer cells, such as breast cancer, lung cancer, melanoma, ovarian cancer, and prostate cancer, but are expressed at very low levels in normal cells or tissues [58-60]. Nanomaterials conjugated to PKCα (FKKQGSFAKKK)- or PKA (ALRRSLG)-specific peptides showed a higher targeting efficacy to cancer cells or tissues than to normal cells or tissues [61-66].

As mentioned in 19.2.2.1., caspase activation in cancer cells is very low, but can be stimulated by the activation of death receptors through stimulators such as TNFα and TRAIL. Caspases induce cell apoptosis by cleavage of their target peptides [30-32]. In a recent study, doxorubicin conjugated to a caspase-3-specific peptide (DEVD) was efficiently cleaved in apoptotic regions of cancer cells induced by radiation exposure, leading to efficient inhibition of cancer growth, with low toxicity in normal tissues [67].

Several protease cleavable nanoparticles have been developed for cancer cell-targeted therapy. Matrix metalloproteinases (MMPs) (MMP-2, -9, and -12) are known as cancer-associated proteases, and participate in the progression of several cancer mechanisms, including migration, invasion, metastasis, and angiogenesis [68,69]. MMP-specific peptides (PVGLIG and GPLGIAGQ for MMP-2) can be selectively cleaved by MMPs that are overexpressed in cancer

cells. Exploiting these functions of MMPs, conjugates of MMP-cleavage peptides and anticancer drugs can be useful for cancer cell-targeted therapies [70-73]. For example, a self-assembled nanoparticle containing PEG 2000-paclitaxel-MMP-2 peptide (GPLGIAGQ) exhibited a higher anticancer efficacy *in vitro* and *in vivo* than did free paclitaxel [70]. Furthermore, nanocages conjugated with a MMP-2-binding peptide (CTTHWGFTLC) showed selective uptake into MMP-2 overexpressing cancer cells [74].

19.2.2.3. Nanomaterials targeting hypoxic cancer regions

EPR-mediated or ligand-mediated targeting methods generally have a low targeting efficacy for hypoxic tumor regions. Their therapeutic efficacy against hypoxic tumor cells is also dramatically reduced because of the limited delivery of therapeutic agents to cancer cells and the induction of drug resistance [75,76].

Hypoxia-inducible factor-1α (HIF-1α) is an attractive therapeutic target because it is a key regulator of the hypoxic environment and is related to drug resistance and cancer metastasis [76]. Therefore, suppression of HIF-1α expression leads to an increase in therapeutic efficacy against hypoxic cancer cells. Several nanomaterials that bind to or contain HIF-1α siRNA or antisense oligonucleotides have been developed and have exhibited a high therapeutic efficacy for hypoxic cancer cells and increased inhibitory efficacy against cancer metastasis [77-80].

For hypoxic cancer cell-targeted therapy, several nanomaterials (mainly viral nanomaterials) incorporating hypoxia-responsive promoters that are specifically expressed in hypoxic cancers, have a high specificity and gene expression for hypoxic cancer cells [81,82]. Furthermore, nanomaterials containing hypoxia-responsive agents (2-nitroimidazole), which can be highly sensitive to hypoxia, are suitable for hypoxic tumor cell-targeted therapy [83,84].

Another strategy for hypoxic cancer cell-targeted therapy is the use of anaerobic bacteria (*e.g., Salmonella* and *Clostridium spp.*). Anaerobic bacteria themselves have the capacity to inhibit the growth of cancer cells and also can increase therapeutic efficacy in combination with anticancer molecules or radiation therapy [13,85-88]. *Salmonella* and *Clostridium* are pathogenic bacteria and therefore cause clinical safety problems such as inflammation and immune responses. To overcome these problems, non-pathogenic anaerobic bacteria (*e.g. Bifidobacterium sp.*) [89] and nonpathogenic or attenuated bacteria [90,91] are being developed as bacterial vectors to target hypoxic cancers.

19.3. CLINICAL APPLICATIONS OF NANOMATERIALS IN CANCER TREATMENT

Nanomaterial-anticancer drug complexes are most commonly used in cancer clinical trials. For example, liposomes loaded with anticancer drugs, such as doxorubicin and daunorubicin, have been approved by the U.S. Food and Drug Administration for the treatment of several cancers, such as ovarian and metastatic breast and human immunodeficiency virus-related Kaposi sarcoma (see [93–95] for review). In cancer clinical trials, the use of PEG-conjugated liposomes (rather than PEG-free liposomes) may be a more efficient way to increase therapeutic effects of anticancer drugs, because of their prolonged blood circulation time and enhanced drug accumulation in cancer cells [94,95]. In addition to liposome-drug complexes, several nanomaterial-drug complexes are currently undergoing clinical trials in cancer, such as the polymer-drug conjugate of paclitaxel and poly(L-glutamic acid) (also known as paclitaxel poliglumex, Xyotax, and CT-2103) for the treatment of non-small cell lung cancer [96,97], cyclodextrin-PEG micelle with camptothecin (also known as CRLX-101) for advanced (metastatic and / or unresectable) solid malignancies [98] and PEG-irinotecan conjugate (also known as etirinotecan pegol and NKTR-102) for advanced breast cancer [99]. Targeting delivery of these nanomaterial-drug complexes to cancer cells is based on the EPR effect.

On the other hand, there are very few reports on cancer clinical trials using nanomaterial-gene complexes. Recently, results of a phase I clinical trial using a complex of the human tumor suppressor gene p53 with a liposomal nanomaterial (SGT-53) employing an anti-transferrin receptor single-chain antibody fragment (scFv) as the targeting molecule were reported. The trial supplied evidence of targeted cancer delivery of systemically dosed SGT-53 to metastatic lesions. Furthermore, SGT-53 was well-tolerated and exhibited anticancer activity [100]. Similarly, in a phase I clinical trial using a small interfering RNA targeting the M2 subunit of ribonucleotide reductase (RRM2) complexed with nanomaterials containing a cyclodextrin-containing polymer, a PEG, and human transferrin, the complex efficiently reduced the specific RRM2 messenger RNA and the RRM2 protein levels in cancer tissues [101]. Targeting of nanomaterial-gene complexes containing scFv [100] or transferrin [101] to cancers is based on the active cancer targeting method, and takes advantage of the overexpression of transferrin receptor in cancer cells.

19.4. SUMMARY AND CONCLUSIONS

For cancer cell-targeted delivery of therapeutic molecules, several delivery systems, including viral or non-viral nanomaterials, and anaerobic bacterial carriers, have been developed and utilized for *in vivo* or *ex vivo* / *in vitro* applications. Cancer targeting by nanomaterials is accomplished by both passive and active cancer targeting. Passive targeting methods based on the EPR effect exhibit low therapeutic efficacy in poorly vascularized regions and in spreading and metastatic cancers. Active cancer targeting is based on the recognition or response to overexpressed receptors, overexpressed intracellular signals, and hypoxic regions in cancer cells and tissues. However, a lack of cancer targeting materials (ligands and peptide substrates responding to activated receptors and intracellular signals, respectively) and different activity levels of receptors and intracellular signals between patients may be a serious obstacle to be overcome for the use of nanomaterials based on the active cancer targeting method.

Table 2. Receptor-specific ligands used for the development of cancer cell-targeted nanomaterials

Ligands	Receptors	Target cancer cells	Refs.
Antibodies (Abs)			
Anti-CD20 Ab (Mabthera)	CD20 receptor	Daudi lymphoma cells	[102]
Anti-CD71 Ab	TfR	PC-3 human prostate cancer cells	[103]
Anti-DR5 Ab	Death receptor 5 (DR5; also known as TRAIL-receptor 2)	HCT116 human colon cancer cells	[104]
		A375 human melanoma cells	[105]
Anti-HER2 Ab (Herceptin)	Human epidermal growth factor receptor 2 (HER2)	SKOV-3 human ovarian cancer cells	[102]
		SK-BR-3 human breast cancer cells	[106]
Anti-Met Ab	Hepatocyte growth factor receptor (HGFR; also known as c-Met or Met)	A549 human lung cancer and MKN45 human gastric cancer cells	[107]
Single chain variable fragment anti-EGFR Ab (ScFvEGFR)	EGFR	H292 human lung cancer cells	[108]
Transferrin receptor Ab (OKT9)	TfR	Ramos human Burkitt's lymphoma cells	[109]

Ligands	Receptors	Target cancer cells	Refs.
Aptamers			
Sgc8 DNA aptamer	PTK7 (an orphan tyrosine kinase receptor)	CEM lymphoblastic leukemia cells	[110]
GL21.T aptamer	Axl receptor (a tyrosine kinase receptor)	A549 human lung cancer and U87 human glioma cells	[111]
GS24 aptamer	TfR	B16 mouse melanoma cells	[112]
Proteins (glycoproteins)			
Asialofetuin	Asialoglycoprotein receptor	HepG2 human hepatocellular carcinoma cells	[113]
EGF	EGFR	H22 mouse hepatocellular carcinoma cells	[114]
		MDA-MB-468 human breast cancer cells	[115]
		A431 human epidermoid carcinoma cells	[116]
EphrinA I	EphA2 receptor	PC-3 human prostate cancers	[117]
Transferrin (apotransferrin)	TfR	K562 human leukemia cells	[118]
		K562 > MV4-11 > Raji human leukemia cells	[44]
		LLC1 mouse lung cancer cells	[119]
		ZH5 rat hepatocellular carcinoma cells	[120]
		Ramos human Burkitt's lymphoma cells	[109]
		HepG2 human hepatocellular carcinoma cells	[121]
		SCC-7 murine squamous cell carcinoma cells	[122]
Urokinase plasminogen activator (uPA)	uPA receptor (uPAR)	MIA PaCa-2 human pancreatic cancer cells	[123]
VEGF121	VEGF receptor	U87 human glioma cells	[124]

Ligands	Receptors	Target cancer cells	Refs.
Peptides			
Analogue peptide of neuropeptide Y (Arg6, Pro34)	Y1-receptor	MCF-7 human breast cancer cells	[125]
Angiopep-2 (TFFYGGSRGKRNNFKTEEY)	Low-density lipoprotein receptor-related protein-1	C6 rat glioma / U87 human glioma cells	[126]/ [127]
α-conotoxin ImI	α7 nicotinic acetylcholine receptor (α7 nAChR)	MCF-7 human breast cancer cells	[128]
α-melanocyte-stimulating hormone peptide (SYSMEHFRWGKPV)	Melanocortin type 1 receptor	B16F0 mouse melanoma cells	[129]
apoA-1 mimetic peptide (AP) (FAEKFKEAVKDYFAKFWD)	EGFR	KB human epidermoid carcinoma cells	[130]
ATF peptide (amino acids 1 to 135 of mouse uPA)	uPAR	MIA PaCa-2 human pancreatic cancer cells	[131]
Bombesin (BN) peptide (QWAVGHL)	Gastrin releasing peptide receptor	HeLa human epidermoid carcinoma cells	[132]
Chlorotoxin [a 36-amino acid peptide derived from *Leiurus quinquestriatus* (scorpion) venom]	MMP-2 and receptor-associated protein ClC-3	U89 human glioma/C6 rat glioma cells	[133]/ [134]
		4T1 mouse metastatic breast cancer cells	[135]
Cyclic RGD	Integrin $\alpha_v\beta_3$	M21 human melanoma cells	[136, 137]
		LNCaP human prostate cancer cells	[137]
		SW620 human colon cancer cells	[138]
		U87 human glioma cells	[139]
C16Y peptide (DFKLFAVYIKYR)	Integrin $\alpha_v\beta_3$	B16 mouse melanoma cells	[140]
(D-Lys6)-LHRH	Luteinizing hormone-releasing hormone (LHRH) receptor	A2780 human ovarian cancer cells	[141]
Follicle-stimulating hormone (FSH) β 81–95 peptide	FSH receptor	Caov-3 human ovarian cancer cells	[142]
F3 peptide (KDEPQRRSARLSAKPAPPK	Nucleolin receptor	MDA-MB-435S, MDA-MB-231, and Hs578T	[143]

Ligands	Receptors	Target cancer cells	Refs.
PEPKPKKAPAKK)		human breast cancer cells	
Gastrin (modified peptide; CKSSEAYGW-Nle-DF)	Cholecystokinin-2 receptor	InR1G9 hamster glucagonoma cells	[144]
GE11 peptide (CYHWYGYTPQNVI)	EGFR	HuH7 human hepatocellular carcinoma cells	[145]
HAIYPRH (knor-specific peptide)	TfR	Bel-7402 human hepatocellular carcinoma/U87 human glioma cells	[146]/ [147]
Human ATF (hATF) peptide of uPA	uPAR	MIA PaCa-2 human pancreatic cancer cells	[148]
Interleukin 13 (IL-13) peptide (isolated by phage display; CGEMGWVRC)	IL-13Rα2	U87 human glioma/C6 rat glioma cells	[149]/ [150]
iRGD (neuropilin 1-binding peptide; CRGDKGPDC)	Neuropilin 1	AsPC-1 human pancreatic cancer cells	[151]
MC1R agonist peptide (SYS-Nle-EH-*d*-FRWGKPV)	Melanocortin type-1 receptor (MC1R)	B16F0 / M3 mouse melanoma cells	[152]/ [153]
NR7 peptide (NSVRGSR)	EGFR	SKOV-3 human ovarian cancer cells	[154]
PreS1-derived peptide	Asialoglycoprotein receptor	HepaRG human hepatocellular carcinoma cells	[155]
RGD	Vascular endothelial growth factor receptor-2 (VEGF R2)	N2A mouse neuroblastoma cells	[156]
RGDGSSV	Integrin $\alpha_{2b}\beta_3$	GL261 mouse glioma cell / B16F0 mouse melanoma cells	[157]
YCDGFYACYMDV	HER2	SK-BR-3 human breast cancer cells	[158]
YCDPC	Integrin $\alpha_4\beta_1$	KCl-H929 and MM.1S human multiple myeloma cells	[158]
YIGSR (laminin-derived peptide)	Laminin receptor	B16 mouse melanoma cells	[159]

Ligands	Receptors	Target cancer cells	Refs.
YSA peptide (YSAYPDSVPMMS; mimics the ligand ephrin-A1)	EphA2 receptor	HEY human ovarian cancer cells	[160]
Others (small molecules)			
Anisamide	Sigma receptor	NCI-H460 human lung cancer cells	[161]
		B16F0 mouse melanoma cells	[162]
		H460 human non-small lung cancer cells	[163]
Chondroitin sulfate	CD44 receptor	B16F0 mouse melanoma cells	[164]
Folate	Folate receptor	KB human epidermoid carcinoma cells	[37-39]
		HeLa human epidermoid carcinoma cells	[39]
		9L / LacZ rat gliosarcoma cells	[33]
		IGROV-1 /SKOV-3 human ovarian cancer cells	[34]/ [35]
		B16 mouse melanoma cells	[36]
Galactose / Galactosamine	Asialoglycoprotein receptor	HepG2 human hepatocellular carcinoma cells	[165]/ [166]
Hyaluronic acid	CD44 receptor	SKOV-3TR human ovarian cancer cells	[167]
Lactose	Asialoglycoprotein receptor	HepG2 human hepatocellular carcinoma cells	[168]
NeuAcα2-6Gal (residue of glycoprotein glycan)	CD22	Daudi human B-cell lymphoma cells	[169]
Pectin	Asialoglycoprotein receptor	HepG2 human hepatocellular carcinoma cells	[170]

Ligands	Receptors	Target cancer cells	Refs.
Tamoxifen derivative	Estrogen receptor	MCF-7 human breast cancer cells	[171]
Tetraiodothyroacetic acid ($\alpha_v\beta_3$−antagonist)	Integrin $\alpha_v\beta_3$	A375 human melanoma cells	[172]

ACKNOWLEDGEMENTS

This work was supported by a Health Labour Sciences Research Grant (Research on Publicly Essential Drugs and Medical Devices) from the Ministry of Health, Labour and Welfare of Japan; Special Coordination Funds for Promoting Science and Technology (SCF funding program "Innovation Center for Medical Redox Navigation"), and a Grant-in Aid for Scientific Research (No. 24300172) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES

1. B.W. Stewart, C.P. Wild, *World Cancer Report 2014*, IARC Publisher, Lyon, France, 2014, p. 16.
2. J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray. *Int. J. Cancer* **136** (2015) E359–E386.
3. M. Vanneman, G. Dranoff. *Nat. Rev. Cancer* **12** (2012) 237–251.
4. R. Baskar, K.A. Lee, R. Yeo, K.W. Yeoh. *Int. J. Med. Sci*. **9** (2012) 193–199.
5. V.T. DeVita. *Cancer Res.* **68** (2008) 8643–8653.
6. J.H. Kang, R. Toita, Y. Katayama. *Biotechno. Adv*. **28** (2012) 757–763.
7. S. Biswas, V.P. Torchilin. *Adv. Drug Deliv. Rev*. **66** (2014) 26–41.
8. S.A. Collines, B.A. Guinn, P.T. Harrison, M.F. Scallan, G.C. O'Sullivan, M. Tangney. *Curr. Gene Ther*. **8** (2008) 866–878.
9. M.Z.I. Pranjol, A. Hajitou. *Viruses* **7** (2015) 268–284.
10. R. Waehler, S.J. Russell, D.T. Curiel. *Nat. Rev. Genetics* **8** (2007) 573–587.
11. Y. Zhang, A. Satterlee, L. Huang. *Mol. Ther*. **20** (2012) 1298–1304.
12. X. Guo, L. Huang. *Acc. Chem. Res*. **45** (2012) 971–979.
13. N. Nair, T. Kasai, M. Seno. *Anticancer Res*. **34** (2014) 6289–6296.
14. R.S. Kerbel. *N. Engl. J. Med*. **358** (2008) 2039–2049.
15. S.M. Weis, D.A. Cheresh. *Nat. Med*. **17** (2011) 1359–1370.
16. Y. Matsumura, H. Maeda. *Cancer Res*. **46** (1986) 6387–6392.
17. U. Prabhakar, H. Maeda, R.K. Jain, E.M. Sevick-Muraca, W. Zamboni, O.C. Farokhzad, S.T. Barry, A. Gabizon, P. Grodzinski, D.C. Blakey. *Cancer Res*. **73** (2013) 1–6.
18. M. Longmire, P.L. Choyke, H. Kobayashi. *Nanomedicine* **3** (2008) 703–717.
19. H. Kobayashi, R. Watanabe, P.L. Choyke. *Theranostics* **4** (2014) 81–89.

20. H. Maeda H. Nakamura, J. Fang. *Adv. Drug Deliv. Rev*. **65** (2013) 71–79.
21. H.S. Choi, W. Liu, P. Misra, E. Tanaka, J.P. Zimmer, B. Itty Ipe, M.G. Bawendi, J.V. Frangioni. *Nat. Biotechnol*. **25** (2007) 1165–1170.
22. F. Yuan, M. Dellian, D. Fukumura, M. Leunig, D.A. Berk, V.P. Torchilin, R.K. Jain. *Cancer Res*. **55** (1995) 3752–3756.
23. T.M. Allen, P.R. Cullis. *Science* **303** (2004) 1818–1822.
24. Y. Noguchi, J. Wu, R. Duncan, J. Strohalm, K. Ulbrich, T. Akaike, H. Maeda. *Jpn. J. Cancer Res*. **89** (1998) 307–314.
25. H. Imoto, Y. Sakamura, K. Ohkouchi, R. Atsumi, Y. Takakura, H. Sezaki, M. Hashida. *Cancer Res*. **52** (1992) 4396–4401.
26. C. He, Y. Hu, L. Yin, C. Tang, C. Yin. *Biomaterials* **31** (2010) 3657–3666.
27. E. Zwick, J. Bange, A. Ullrich. *Endocr. Relat. Cancer* **8** (2001)161–173.
28. A. Tomas, C.E. Futter, E.R. Eden. *Trends Cell Biol*. **24** (2014) 26–34.
29. R.T. Dorsam, J.S. Gutkind. *Nat. Rev. Cancer* **7** (2007) 79–94.
30. S. Wang , W.S. Ei-Deiry. *Oncogene* **22** (2003) 8628–8633.
31. K.M. Debatin, P.H. Krammer. *Oncogene* **23** (2004) 2950–2966.
32. M.E. Guicciardi, G.J. Gores. *FASEB J*. **23** (2009) 1625–1637.
33. K.M. McNeeley, E. Karathanasis, A.V. Annapragada, R.V. Bellamkonda. *Biomaterials* **30** (2009) 3986–3995.
34. N. Kamaly, T. Kalber, M. Thanou, J.D. Bell, A.D. Miller. *Bioconjug. Chem*. **20** (2009) 648–655.
35. J.C. Fernandes, X. Qiu, F.M. Winnik, M. Benderdour, X. Zhang, K. Dai, Q. Shi. *Int. J. Nanomedicine* **7** (2012) 5833–5845.
36. L. Wang, M. Li, N. Zhang. *Int. J. Nanomedicine* **7** (2012) 3281–3294.
37. P.J. Stevens, M. Sekido, R.J. Lee. *Pharm. Res*. **21** (2004) 2153–2157.
38. R. Rossin, D. Pan, K. Qi, J.L. Turner, X. Sun, K.L. Wooley, M.J. Welch. *J. Nucl. Med*. **46** (2005) 1210–1218.
39. G. Destito, R. Yeh, C.S. Rae, M.G. Finn, M. Manchester. *Chem Biol*. **14** (2007) 1152–1162.
40. A.J. Ditto, K.N. Shah, N.K. Robishaw, M.J. Panzner, W.J. Youngs, Y.H. Yun. *Mol. Pharm*. **9** (2012) 3089–3098.
41. F. Gao, L. Li, T. Liu, N. Hao, H. Liu, L. Tan, H. Li, X. Huang, B. Peng, C. Yan, K. Yang, X. Wu, D. Chen, F. Tang. *Nanoscale* **4** (2012) 3365–3372.
42. K.D. Lee, S.H. Choi, D.H. Kim, H.Y. Lee, K.C. Choi. *Arch. Pharm. Res*. **37** (2014) 1546–1553.
43. Y.Q. Guan, Z. Zheng, Z. Huang, Z. Li, S. Niu, J.M. Liu. *Sci. Rep*. **4** (2014) 4990.
44. X. Yang, C.G. Koh, S. Liu, X. Pan, R. Santhanam, B. Yu, Y. Peng, J. Pang, S. Golan, Y. Talmon, Y. Jin, N. Muthusamy, J.C. Byrd, K.K. Chan, L.J. Lee, G. Marcucci, R.J. Lee. *Mol. Pharm*. **6** (2009) 221–230.
45. A. Gautam, P. Kapoor, K Chaudhary, R. Kumar; Open Source Drug Discovery Consortium, G. P. Raghava. *Curr. Med. Chem*. **21** (2014) 2367–2391.
46. J. Bábíčková, Ľ. Tóthová, P. Boor, P. Celec. *Biotechnol. Adv*. **31** (2013) 1247–1259.
47. A. Rivinoja, P. Laakkonen. *Methods Mol. Biol*. **683** (2011) 401–415.
48. R. Toita, M. Murata, S. Tabata, K. Abe, S. Narahara, J.S. Piao, J.H. Kang, M. Hashizume. *Bioconjug. Chem*. **23** (2012) 1494–1501.
49. F. Jing, D. Li, W. Xu, Y. Liu, K. Wang, Z. Sui. *Pharm. Biol*. **52** (2014) 570–574.
50. Q. Xu, Y. Liu, S. Su, W. Li, C. Chen, Y. Wu. *Biomaterials* **33** (2012) 1627–1639.

51. X. Li, H. Zhou, L. Yang, G. Du, A.S. Pai-Panandiker, X. Huang, B. Yan. *Biomaterials* **32** (2011) 2540–2545.
52. H. Gao, Y. Xiong, S. Zhang, Z. Yang, S. Cao, X. Jiang. *Mol. Pharm*. **11** (2014) 1042–1052.
53. D.B. Kirpotin, D.C. Drummond, Y. Shao, M.R. Shalaby, K. Hong, U.B. Nielsen, J.D. Marks, C.C. Benz, J.W. Park. *Cancer Res*. **66** (2006) 6732–6740.
54. D.W. Bartlett, H. Su, I.J. Hildebrandt, W.A. Weber, M.E. Davis. *Proc. Natl. Acad. Sci. USA* **104** (2007) 15549–15554.
55. C.H. Choi, C.A. Alabi, P. Webster, M.E. Davis. *Proc. Natl. Acad. Sci. USA* **107** (2010) 1235–1240.
56. C. López-Otín, T. Hunter. *Nat. Rev. Cancer* **10** (2010) 278–292.
57. P.J. Utz, P. Anderson. *Cell Death Differ*. **7** (2000) 589–602.
58. O. Konopatskaya, A.W. Poole. *Trends Pharmacol. Sci*. **31** (2010) 8–14.
59. J.H. Kang. *New J. Sci*. **2014** (2014) 231418.
60. S. Naviglio, M. Caraglia, A. Abbruzzese, E. Chiosi, D. Di Gesto, M. Marra, M. Romano, A. Sorrentino, L. Sorvillo, A. Spina, G. Illiano. *Expert. Opin. Ther. Targets* **13** (2009) 83–92.
61. J.H. Kang, D. Asai, J.H. Kim, T. Mori, R. Toita, T. Tomiyama, Y. Asami, J. Oishi, Y.T. Sato, T. Niidome, B. Jun, H. Nakashima, Y. Katayama. *J. Am. Chem. Soc*. **130** (2008) 14906–14907.
62. J.H. Kang, J. Oishi, J.H. Kim, M. Ijuin, R. Toita, B. Jun, D. Asai, T. Mori, T. Niidome, K. Tanizawa, S. Kuroda, Y. Katayama. *Nanomedicine* **6** (2010) 583–589.
63. R. Toita, J.H. Kang, J.H. Kim, T. Tomiyama, T. Mori, T. Niidome, B. Jun, Y. Katayama. *J. Control. Release* **139** (2009) 133–139.
64. R. Toita, J.H. Kang, T. Tomiyama, C.W. Kim, S. Shiosaki, T. Niidome, T. Mori, Y. Katayama. *J. Am. Chem. Soc.* **134** (2012) 15410–15417.
65. T. Tomiyama, R. Toita, J.H. Kang, D. Asai, S. Shiosaki, T. Mori, T. Niidome, Y. Katayama. *J. Control. Release* **148** (2010) 101–105.
66. J. Oishi, K. Kawamura, J.H. Kang, K. Kodama, T. Sonoda, M. Murata, T. Niidome, Y. Katayama. *J. Control. Release* **110** (2006) 431–436.
67. B.S. Lee, Y.W. Cho, G.C. Kim, D.H. Lee, C.J. Kim, H.S. Kil, D.Y. Chi, Y. Byun, S.H. Yuk, K. Kim, I.S. Kim, I.C. Kwon, S.Y. Kim. *J. Natl. Cancer Inst.* In press. doi: 10.1093/jnci/dju403.
68. K. KIessenbrock, V. Plaks, Z. Werb. *Cell* **141** (2010) 52–67.
69. C. Gialeli, A.D. Theocharis, N. Karamanos. *FEBS J*. **278** (2011) 16–27.
70. L. Zhu, T. Wang, F. Perche, A. Taigind, V.P. Torchilin. *Proc. Natl. Acad. Sci. USA* **110** (2013) 17047–17052.
71. D. Bacinello, E. Garanger, D. Taton, K.C. Tam, S. Lecommandoux. *Biomacromolecules* **15** (2014) 1882–1888.
72. C. Nazli, G.S. Demirer, Y. Yar, H.Y. Acar, S. Kizilel. *Colloids Surf. B Biointerfaces* **122** (2014) 674–683.
73. F.B. Cui, R.T. Li, Q. Liu, P.Y. Wu, W.J. Hu, G.F. Yue, H. Ding, L.X. Yu, X.P. Qian, B.R. Liu. *Cancer Lett*. **346** (2014) 53–62.
74. T. Kawano, M. Murata, J.S. Piao, S. Narahara, N. Hamano, J.H. Kang, M. Hashizume. *Int. J. Mol. Sci*. **16** (2015) 148–158.
75. W.R. Wilson, M.P. Hay. *Nat. Rev. Cancer* **11**, (2011) 393–410.
76. J.M. Brown, W.R. Wilson. *Nat. Rev. Cancer* **4** (2004) 437–447.
77. X. Zhao, F. Li, Y. Li, H. Wang, H. Ren, J. Chen, G. Nie, J. Hao. *Biomaterials* **46** (2015) 13–25.

78. X.Q. Liu, M.H. Xiong, X.T. Shu, R.Z. Tang, J. Wang. *Mol. Pharm*. **9** (2012) 2863–2874.
79. W.H. Chen, R.L. Lecaros, Y.C. Tseng, L. Huang, Y.C. Hsu. *Cancer Lett*. **359** (2015) 65–74.
80. Y. Wang, M. Saad, R.I. Pakunlu, J.J. Khandare, O.B. Garbuzenko, A.A. Vetcher, V.A. Soldatenkov, V.P. Pozharov, T. Minko. *Clin. Cancer Res*. **14** (2008) 607–616.
81. R.L. Cowen, E.J. Garside, B. Fitzpatrick, M.V. Papadopoulou, K.J. Williams. *Br. J. Radiol*. **81** (2008) S45–S56.
82. P.B. Card, R.T. Hogg, C.R. Gil Del Alcazar, R.D. Gerard. *Cancer Gene Ther*. **19** (2012) 451–459.
83. T. Thambi, V.G. Deepagan, H.Y. Yoon, H.S. Han, S.H. Kim, S. Son, D.G. Jo, C.H. Ahn, Y.D. Suh, K. Kim, I.C. Kwon, D.S. Lee, J.H. Park. *Biomaterials* **35** (2014) 1735–1743.
84. O. Mazuryk, M. Maciuszek, G. Stochel, F. Suzenet, M. Brindell. *J. Inorg. Biochem*. **134** (2014) 83–91.
85. C. Bettegowda, L.H. Dang, R. Abrams, D.L. Huso, L. Dillehay, I. Cheong, N. Agrawal, S. Borzillary, K.M. McCaffery, E.L. Watson, K.S. Lin, F. Bunz, K. Baidoo, M.G. Pomper, K.W. Kinzler, B. Vogelstein, S. Zhou. *Proc. Natl. Acad. Sci. USA* **9** (2003) 15083–15088.
86. C.H. Lee, C.L. Wu, Y.S. Tai, A.L. Shiau. *Mol. Ther*. **11** (2005) 707–716.
87. M.Q. Wei, R. Ren, D. Good, J. Anné. *Genet. Vaccines Ther*. **6** (2008) 8.
88. B. Yu, M. Yang, L. Shi, Y. Yao, Q. Jiang, X. Li, L. H. Tang, B.J. Zheng, K.Y. Yuen, D.K. Smith, E. Song, J.D. Huang. *Sci. Rep*. **2** (2012) 436.
89. S. Taniguchi, M. Fujimori, T. Sasaki, H. Tsutsui, Y. Shimatani, K. Seki, J. Amano. *Cancer Sci*. **101** (2010) 1925–1932.
90. K.B. Low, M. Ittensohn, T. Le, J. Platt, S. Sodi, M. Amoss, O. Ash, E. Carmichael, A. Chakraborty, J. Fischer, S.L. Lin, X. Luo, S.I. Miller, L. Zheng, I. King, J.M. Pawelek, D. Bermudes. *Nat. Biotechnol*. **17** (1999) 37–41.
91. V. Punj, D. Saint-Dic, S. Daghfal, J.R. Kanwar. *Cancer Biol. Ther*. **3** (2004) 708–714.
92. T. Mori, J.H. Kang, in *Breakthroughs in melanoma research*, Y. Tanaka (Ed.), InTech Publisher, Rijeka, Croatia, 2012, p. 389.
93. A.S. Thakor, S.S. Gambhir. *CA Cancer J. Clin*. **63** (2013) 395–418.
94. R.K. Jain, T. Stylianopoulos. *Nat. Rev. Clin. Oncol*. **7** (2010) 653–664.
95. Y. Barenholz. *J. Control. Release* **160** (2012) 117–134.
96. L. Paz-Ares, H. Ross, M. O'Brien, A. Riviere, U. Gatzemeier, J. Von Pawel, E. Kaukel, L. Freitag, W. Digel, H. Bischoff, R. García-Campelo, N. Iannotti, P. Reiterer, I. Bover, J. Prendiville, A.J. Eisenfeld, F.B. Oldham, B. Bandstra, J.W. Singer, P. Bonomi. *Br. J. Cancer* **98** (2008) 1608–1613.
97. M.E. O'Brien, M.A. Socinski, A.Y. Popovich, I.N. Bondarenko, A. Tomova, B.T. Bilynsky, Y.S. Hotko, V.L. Ganul, I.Y. Kostinsky, A.J. Eisenfeld, L. Sandalic, F.B. Oldham, B. Bandstra, A.B. Sandler, J.W. Singer. *J. Thorac. Oncol*. **3** (2008) 728–734.
98. G.J. Weiss, J. Chao, J.D. Neidhart, R.K. Ramanathan, D. Bassett, J.A. Neidhart, C.H. Choi, W. Chow, V. Chung, S.J. Forman, E. Garmey, J. Hwang, D.L. Kalinoski, M. Koczywas, J. Longmate, R.J. Melton, R. Morgan, J. Oliver, J.J. Peterkin, J.L. Ryan, T. Schluep, T.W. Synold, P. Twardowski, M.E. Davis, Y. Yen. *Invest. New Drugs* **31** (2013) 986–1000.

99. A. Awada, A.A. Garcia, S. Chan, G.H. Jerusalem, R.E. Coleman, M.T. Huizing, A. Mehdi, S.M. O'Reilly, J.T. Hamm, P.J. Barrett-Lee, V. Cocquyt, K. Sideras, D.E. Young, C. Zhao, Y.L. Chia, U. Hoch, A.L. Hannah, E.A. Perez. *Lancet Oncol*. **14** (2013) 1216–1225.
100. N. Senzer, J. Nemunaitis, D. Nemunaitis, C. Bedell, G. Edelman, M. Barve, R. Nunan, K.F. Pirollo, A. Rait, E.H. Chang. *Mol. Ther.* **21** (2013) 1096–1103.
101. M.E. Davis, J.E. Zuckerman, C.H. Choi, D. Seligson, A. Tolcher, C.A. Alabi, Y. Yen, J.D. Heidel, A. Ribas. *Nature* **464** (2010)1067–1070.
102. A. Cirstoiu-Hapca, L. Bossy-Nobs, F. Buchegger, R. Gurny, F. Delie. *Int. J. Pharm*. **331** (2007) 190–196.
103. A.E. Felber, B. Castagner, M. Elsabahy, G.F. Deleavey, M.J. Damha, J.C. Leroux. *J. Control. Release* **152** (2011) 159–167.
104. S.M. Abdelghany, D. Schmid, J. Deacon, J. Jaworski, F. Fay, K.M. McLaughlin, J.A. Gormley, J.F. Burrows, D.B. Longley, R.F. Donnelly, C.J. Scott. *Biomacromolecules* **14** (2013) 302–310.
105. B. Ding, X. Wu, W. Fan, Z. Wu, J. Gao, W. Zhang, L. Ma, W. Xiang, Q. Zhu, J. Liu, X. Ding, S. Gao. *Int. J. Nanomedicine* **6** (2011) 1991–2005.
106. Y. Liu, K. Li, B. Liu, S.S. Feng. *Biomaterials* **31** (2010) 9145–9155.
107. R. Heukers, I. Altintas, S. Raghoenath, E. De Zan, R. Pepermans, R.C. Roovers, R. Haselberg, W.E. Hennink, R.M. Schiffelers, R.J. Kok, P.M. van Bergen en Henegouwen. *Biomaterials* **35** (2014) 601–610.
108. X.H. Peng, Y. Wang, D. Huang, Y. Wang, H.J. Shin, Z. Chen, M.B. Spewak, H. Mao, X. Wang, Y. Wang, Z.G. Chen, S. Nie, D.M. Shin. *ACS Nano* **5** (2011) 9480–9493.
109. J. Wang, S. Tian, R.A. Petros, M.E. Napier, J.M. Desimone. *J. Am. Chem. Soc*. **132** (2010) 11306–11313.
110. T. Chen, M.I. Shukoor, R. Wang, Z. Zhao, Q. Yuan, S. Bamrungsap, X. Xiong, W. Tan. *ACS Nano* **5** (2011) 7866–7873.
111. L. Cerchia, C.L. Esposito, S. Camorani, A. Rienzo, L. Stasio, L. Insabato, A. Affuso, V. de Franciscis. *Mol. Ther*. **20** (2012) 2291–303.
112. M.Z. Zhang, R.N. Yu, J. Chen, Z.Y. Ma, Y.D. Zhao. *Nanotechnology* **23** (2012) 485104.
113. S. Díez, G. Navarro, C.T. de ILarduya. *J. Gene Med.* **11** (2009) 38–45.
114. Y.C. Yao, X.Y. Zhan, J. Zhang, X.H. Zou, Z.H. Wang, Y.C. Xiong, J. Chen, G.Q. Chen. *Biomaterials* **29** (2008) 4823–4830.
115. M.A. Sandoval, B.R. Sloat, D.S. Lansakara, A. Kumar, B.L. Rodriguez, K. Kiguchi, J. Digiovanni, Z. Cui. *J. Control. Release* **157** (2012) 287–296.
116. C. Fortier, G. De Crescenzo, Y. Durocher. *Biomaterials* **34** (2013) 1344–1353.
117. A.M. Gobin, J.J. Moon, J.L. West. *Int. J. Nanomedicine* **3** (2008) 351–358.
118. N.C. Bellocq, S.H. Pun, G.S. Jensen, M.E. Davis. *Bioconjug. Chem*. **14** (2003) 1122–1132.
119. R.A. Abela, J. Qian, L. Xu, T.S. Lawrence, M. Zhang. *Cancer Gene Ther*. **15** (2008) 496–507.
120. A.D. Krishna, R.K. Mandraju, G. Kishore, A.K. Kondapi. *PLoS One* **4** (2009) e7240.
121. W. Wang, F. Zhou, L. Ge, X. Liu, F. Kong. *Int. J. Nanomedicine* **7** (2012) 2513–2522.
122. J.Y. Yhee, S.J. Lee, S. Lee, S. Song, H.S. Min, S.W. Kang, S. Son, S.Y. Jeong, I.C. Kwon, S.H. Kim, K. Kim. *Bioconjug. Chem*. **24** (2013) 1850–1860.

123. G.Y. Lee, W.P. Qian, L. Wang, Y.A. Wang, C.A. Staley, M. Satpathy, S. Nie, H. Mao, L. Yang. *ACS Nano* **7** (2013) 2078–2089.
124. S. Goel, F. Chen, H. Hong, H.F. Valdovinos, R. Hernandez, S. Shi, T.E. Barnhart, W. Cai. *ACS Appl. Mater. Interfaces* **6** (2014) 21677–21685.
125. W. Hild, K. Pollinger, A. Caporale, C. Cabrele, M. Keller, N. Pluym, A. Buschauer, R. Rachel, J. Tessmar, M. Breunig, A. Goepferich. *Proc. Natl. Acad. Sci. USA* **107** (2010) 10667–10672.
126. R. Huang, W. Ke, L. Han, J. Li, S. Liu, C. Jiang. *Biomaterials* **32** (2011) 2399–2406.
127. L. Mei, Q. Zhang, Y. Yang, Q. He, H. Gao. *Int. J. Pharm*. **474** (2014) 95–102.
128. D. Mei, Z. Lin, J. Fu, B. He, W. Gao, L. Ma, W. Dai, H. Zhang, X. Wang, J. Wang, X. Zhang, W. Lu, D. Zhou, Q. Zhang. *Biomaterials* 42 (2015) 52–65.
129. L. Vannucci, E. Falvo, M. Fornara, P. Di Micco, O. Benada, J. Krizan, J. Svoboda, K. Hulikova-Capkova, V. Morea, A. Boffi, P. Ceci. *Int. J. Nanomedicine* **7** (2012) 1489–1509.
130. Z. Zhang, J. Chen, L. Ding, H. Jin, J.F. Lovell, I.R. Corbin, W. Cao, P.C. Lo, M. Yang, M.S. Tsao, Q. Luo, G. Zheng. *Small* **6** (2010) 430–437.
131. L. Yang, H. Mao, Z. Cao, Y.A. Wang, X. Peng, X. Wang, H.K. Sajja, L. Wang, H. Duan, C. Ni, C.A. Staley, W.C. Wood, X. Gao, S. Nie. *Gastroenterology* **136** (2009) 1514–1525.
132. L. Hosta-Rigau, I. Olmedo, J. Arbiol, L.J. Cruz, M.J. Kogan, F. Albericio. *Bioconjug. Chem*. **21** (2012) 1070–1078.
133. C. Qin, B. He, W. Dai, Z. Lin, H. Zhang, X. Wang, J. Wang, X. Zhang, G. Wang, L. Yin, Q. Zhang. *Biomaterials* **35** (2014) 5908–5920.
134. S. Huang, J. Li, L. Han, S. Liu, H. Ma, R. Huang, C. Jiang. *Biomaterials* **32** (2011) 6832–6838.
135. C. Qin, B. He, W. Dai, H. Zhang, X. Wang, J. Wang, X. Zhang, G. Wang, L. Yin, Q. Zhang. *Mol. Pharm*. **11** (2014) 3233–3241.
136. C.A. Boswell, P.K. Eck, C.A. Regino, M. Bernardo, K.J. Wong, D.E. Milenic, P.L. Choyke, M.W. Brechbiel. *Mol. Pharm*. **5** (2008) 527–539.
137. H.S. Choi, W. Liu, F. Liu, K. Nasr, P. Misra, M.G. Bawendi, J.V. Frangioni. *Nat. Nanotechnol*. **5** (2010) 42–47.
138. L. Li, J. Yang, W.W. Wang, Y.C. Yao, S.H. Fang, Z.Y. Dai, H.H. Hong, X. Yang, X.T. Shuai, G.Q. Gao. *Int. J. Pharm*. **438** (2012) 1–10.
139. Y. Zhong, C. Wang, R. Cheng, L. Cheng, F. Meng, Z. Liu, Z. Zhong. *J. Control. Release* **195** (2014) 63–71.
140. N. Hamano, Y. Negishi, A. Fujisawa, M. Manandhar, H. Sato, F. Katagiri, M. Nomizu, Y. Aramaki. *Int. J. Pharm*. **428** (2012) 114–117.
141. N.V. Nukolova, H.S. Oberoi, Y. Zhao, V.P. Chekhonin, A.V. Kabanov, T.K. Bronich. *Mol. Pharm*. **10** (2013) 3913–321.
142. X. Zhang, J. Chen, Y. Kang, S. Hong, Y. Zheng, H. Sun, C. Xu. *Int. J. Pharm*. **453** (2013) 498–505.
143. V. Moura, M. Lacerda, P. Figueiredo, M.L. Corvo, M.E. Cruz, R. Soares, M.C. de Lima, S. Simões, J.N. Moreira. *Breast Cancer Res. Treat*. **133** (2012) 61–73.
144. C. Sanchez, D. El Hajj Diab, V. Connord, P. Clerc, E. Meunier, B. Pipy, B. Payré, R.P. Tan, M. Gougeon, J. Carrey, V. Gigoux, D. Fourmy. *ACS Nano* **8** (2014) 1350–1363.

145. F.M. Mickler, L. Möckl, N. Ruthardt, M. Ogris, E. Wagner, C. Bräuchle. *Nano Lett*. **12** (2012) 3417–3423.
146. L. Han, R. Huang, J. Li, S. Liu, S. Huang, C. Jiang. *Biomaterials* **32** (2011) 1242–1252.
147. Y. Kuang, S. An, Y. Guo, S. Huang, K. Shao, Y. Liu, J. Li, H. Ma, C. Jiang. *Int. J. Pharm*. **454** (2013) 11–20.
148. Y.S. Cho, G.Y. Lee, H.K. Sajja, W. Qian, Z. Cao, W. He, P. Karna, X. Chen, H. Mao, Y.A. Wang, L. Yang. *Small* **9** (2013) 1964–1973.
149. H. Gao, Z. Yang, S. Zhang, S. Cao, S. Shen, Z. Pang, X. Jiang. *Sci. Rep*. **3** (2013) 2534.
150. B. Wang, L. Lv, Z. Wang, Y. Zhao, L. Wu, X. Fang, Q. Xu, H. Xin. *Biomaterials* **35** (2014) 5897–5907.
151. M. Murata, S. Narahara, T. Kawano, N. Hamano, J.S. Piao, J.H. Kang, K. Ohuchida, T. Murakami, M. Hashizume. *Mol. Pharm*. **12** (2015) 1422–1430.
152. W. Lu, C. Xiong, R. Zhang, L. Shi, M. Huang, G. Zhang, S. Song, Q. Huang, G.Y. Liu, C. Li. *J. Control. Release* **161** (2012) 959–966.
153. M.O. Durymanov, E.A. Beletkaia, A.V. Ulasov, Y.V. Khramtsov, G.A. Trusov, N.S. Rodichenko, T.A. Slastnikova, T.V. Vinogradova, N.Y. Uspenskaya, E.P. Kopantsev, A.A. Rosenkranz, E.D. Sverdlov, A.S. Sobolev. *J. Control. Release* **163** (2012) 211–219.
154. C.W. Liu, W.J. Lin. *Int. J. Nanomedicine* **7** (2012) 4749–4767.
155. M. Murata, J.S. Piao, S. Narahara, T. Kawano, N. Hamano, J.H. Kang, D. Asai, R. Ugawa, M. Hashizume. *Protein Expr. Purif*. **110** (2015) 52–56.
156. R.M. Schiffelers, A. Ansari, J. Xu, Q. Zhou, Q. Tang, G, Storm, G. Molema, P.Y. Lu P.V. Scaria, M.C. Woodle. *Nucleic Acids Res*. **32** (2004) e149.
157. D. Hallahan, L. Geng, S. Qu, C. Scarfone, T. Giorgio, E. Donnelly, X. Gao, J. Clanton. *Cancer Cell* **3** (2003) 63–74.
158. J.F. Stefanick, J.D. Ashley, B. Bilgicer. *ACS Nano* **7** (2013) 8115–8127.
159. G. Sarfati, T. Dvir, M. Elkabets, R.N. Apte, S. Cohen. *Biomaterials* **32** (2011) 152–161.
160. W.H. Blackburn, E.B. Dickerson, M.H. Smith, J.F. McDonald, L.A. Lyon. *Bioconjug. Chem*. **20** (2009) 960–968.
161. S.D. Li, Y.C. Chen, M.J. Hackett, L. Huang. *Mol. Ther*. **16** (2008) 163–169.
162. Y. Yang, J. Li, F. Liu, L. Huang. *Mol. Ther*. **20** (2012) 609–615.
163. S.K. Kim, M.B. Foote, L. Huang. *Cancer Lett*. **334** (2013) 311–318.
164. T. Kurosaki, T. Kitahara, S. Kawakami, K. Nishida, J. Nakamura, M. Teshima, H. Nakagawa, Y. Kodama, H. Sasaki. *Biomaterials* **30** (2009) 4427–4434.
165. F.L. Mi, Y.Y. Wu, Y.L. Chiu, M.C. Chen, H.W. Sung, S.H. Yu, S.S. Shyu, M.F. Huang. *Biomacromolecules* **8** (2007) 892–898.
166. H.F. Liang, C.T. Chen, S.C. Chen, A.R. Kulkarni, Y.L. Chiu, M.C. Chen, H.W. Sung. *Biomaterials* **27** (2006) 2051–2059.
167. X. Yang, A.K. Lyer, A. Singh, E. Choy, F.J. Hornicek, M.M. Amiji, Z. Duan. *Sci. Rep*. **5** (2015) 8509.
168. X. Zhou, M. Zhang, B. Yung, H. Li, C. Zhou, L.J. Lee, R.J. Lee. *Int. J. Nanomedicine* **7** (2012) 5465–5474.
169. W.C. Chen, D.S. Sigal, A. Saven, J.C. Paulson. *Leuk. Lymphoma*. **53** (2012) 208–210.
170. C.Y. Yu, Y.M. Wang, N.M. Li, G.S. Liu, S. Yang, G.T. Tang, D.X. He, X.W. Tan, H. Wei. *Mol. Pharm*. **11** (2014) 638–644.

171. E.C. Dreaden, S.C. Mwakwari, Q.H. Sodji, A.K. Oyelere, M.A. El-Sayed. *Bioconjug. Chem*. **20** (2009) 2247–2253.
172. S. Lee, J. Kim, G. Shim, S. Kim, S.E. Han, K. Kim, I.C. Kwon, Y. Choi, Y.B. Kim, C.W. Kim, Y.K. Oh. *J. Control. Release* **164** (2012) 213–220.