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Nanotechnology in Cancer Therapy: Overview and Applications

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ABSTRACT – Nanotechnology for cancer therapy is playing a pivotal role in dramatically improving current approaches to cancer detection, diagnosis, and therapy while reducing toxic side effects associated with previous cancer therapy. A widespread understanding of these new technologies will lead to develop the more refined design of optimized nanoparticles with improved selectivity, efficacy and safety in the clinical practice of oncology. This review provides an integrated overview of applications and advances of nanotechnology in cancer therapy, based on molecular diagnostics, treatment, monitoring, target drug delivery, approved nanoparticle-based chemotherapeutic agents, and current clinical trials in the development of nanomedicine and ultimately personalized medicine.

Key words – Nanotechnology, Nanomedicine, Nanoparticles, Cancer therapy, Personalized therapy

Nanotechnology is the interdisciplinary field which is focused on man-made materials up to 100×10^{-9} m (Grobmyer et al., 2010). Applications of nanotechnology in the screening, diagnosis, and treatment of disease are collectively referred to as "nanomedicine" – an emerging field that has the potential to revolutionize individual and population-based health in the 21st century (Pautler et al., 2010). In recent years, considerable progress and attention have been made in the design and application of cancer nanotechnology, that is, nanooncology, which is currently the most important chapter of nanomedicine for improving cancer detection, diagnosis, and treatment (Cuenca et al., 2006; Jain, 2010; Misra et al., 2010).

Nanobiotechnology plays an important role in the discovery of biomarkers of cancer as well as the development of several drugs for cancer and aids to cancer surgery (Jain, 2007; Jain, 2010). It also provides a unique approach and comprehensive technology against cancer through early diagnosis, prediction, prevention, personalized therapy and medicine for cancer (Misra et al., 2010). The impact of nanobiotechnology on oncology is shown schematically in Figure 1 (Jain, 2005; Jain, 2007; Jain, 2010). This article will focus our attention on current advances and applications of nanotechnology in cancer therapy for helping with further advancement of developing better cancer drug delivery system that can be applied clinically.

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Nanotechnology in Cancer Detection and Diagnosis

Quantum dots for molecular diagnosis of cancer

Semiconductor quantum dots (QDs) have attracted the considerable interest of many research groups because of their scientific and technological significance in microelectronics, optoelectronics and cellular imaging in recent years (Ferrari, 2005; Nie et al., 2007; Grodzinski et al., 2006; Misra et al., 2010). Semiconductor QDs are emerging as a new class of fluorescent labels for biology and medicine, of which the broad absorption and narrow emission characteristics make it possible to perform multicolor imaging with a single excitation source (Misra et al., 2010). The high fluorescence quantum yield of the QDs, their resistance to photobleaching and their unique physical, chemical and optical properties make them good candidates for fluorescent tagging for in vivo molecular and cellular imaging (Alivisatos, 2004; Gao, et al., 2005; Michalet et al., 2005). The best characteristics of QDs and magnetic iron oxide nanoparticles can be combined to create a single nanoparticle probe that can yield clinically useful images of both tumors and the molecules involved in cancer (Choi et al., 2006; Jain, 2010).

Nanotechnology for detection of cancer biomarkers

From a practical point of view, biomarker would specifically and sensitively reflect a disease state and could be used for diagnosis as well as for disease monitoring during and following therapy (Jain, 2005; Jain, 2010). Nanotechnology has enabled the detection of cancer biomarkers to be further developed. The physicochemical characteristics and high surface

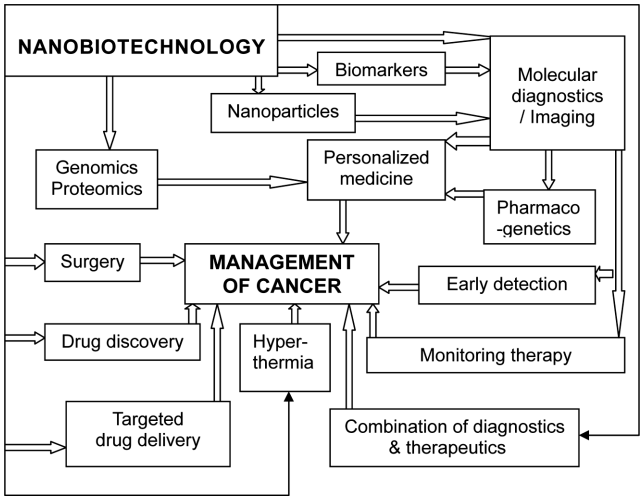

Figure 1. Schematic representation of the role of nanobiotechnology in the management of cancer.

areas of nanoparticles make them ideal candidates for developing platforms for harvesting biomarkers (Gaster et al., 2009; Jain, 2010). A magnetic nanosensor technology is up to 1,000 times more sensitive than any technology now in clinical use, can detect biomarker proteins over a range of concentrations three times broader than any existing method and is accurate regardless of which bodily fluid is being analyzed (Gaster et al., 2009). The nanosensor chip also can search for up to 64 different proteins simultaneously and has been shown to be effective in early detection of tumors in mice, suggesting that it may open the door to significantly earlier detection of even the most elusive cancers in humans (Jain 2007; Jain, 2010).

Targeted Cancer Therapy

In order to achieve many imaging and therapeutic applications in cancer nanotechnology in vivo, nanomaterials must be delivered to sites of cancer (Lammers et al., 2008). For many imaging and therapeutic applications, selective or preferential delivery of nanomaterials to sites of cancer would be optimal (Grobmyer et al., 2010). Two general approaches have been utilized to accomplish this: passive targeting and active targeting (Cho et al., 2008).

Passive targeting

Passive targeting of nanoparticles relies on abnormal gap junctions (100-600 nm) in the endothelium of tumor blood vessels for accumulation of nanoparticles in tumors (Maeda et al., 1989). In order to achieve passive targeting of nanoparticles, engineering of particles with long-circulation half-lives such as coating particles with hydrophilic polymer such as polyethylene glycol (PEG) is most desirable and this type of construct favors passive accumulation of particles inside tumors (Cho et al., 2008; Lammers et al., 2008). In general, small particle size is thought to favor intratumoral extravasation (Yuan, 1995; Kong, 2000). Particle composition and shape are also determinants of particle uptake, although these relationships have not been well characterized (De Jong et al., 2008).

Active targeting

Active targeting of nanoparticles relies on conjugation of a tumorspecific ligand(s) to nanoparticles for specific delivery of nanoparticles to tumor sites (Allen et al., 2002; Black et al., 2008). Targeting moieties that have been investigated include antibodies, peptides, cell surface ligands, and aptamers (Lammers et al., 2008; Cho et al., 2008). Targets in tumors have included tumor antigens, cell surface receptors that are internalized e.g., folate receptors (Santra et al., 2005) and transferrin receptors (Sahoo et al., 2004), and tumor vasculature (Smith et al., 2008). Active targeting has been extensively studied in preclinical models but has not been effectively translated into current clinical applications (Lammers et al., 2008). In preclinical models, targeting has variably led to increased accumulation in tumors (Kirpotin et al., 2006; Park et al., 2004). In many instances, cancer cell uptake has been increased with targeting without increase in overall tumor accumulation of nanoparticles (Kirpotin et al., 2006; Park et al., 2004). Development of novel, specific targeting strategies for nanoparticles to cancer remains an important area of active investigation (Grobmyer et al., 2010).

Targeted Drug Delivery by Nanobiotechnology

Role of nanobiotechnology in therapeutic delivery for cancer

Nanoparticle formulations help to overcome the issue of drug solubility, which is an essential factor for drug effectiveness as well as to facilitate drug delivery across various barriers, the most important of which is the blood-brain barrier, which limits access to brain tumors (Jain, 2007; Jain, 2010). Nanobiotechnologies, mostly based on nanoparticles, have been used to facilitate drug delivery in cancer.

Targeted delivery of biological therapies for cancer

Physical forces such as electric or magnetic fields, ultrasound, hyperthermia or light may contribute to focusing and triggered activation of nanosystem including plasmid DNA,

small interfering RNA (siRNA) and other therapeutic nucleic acids (Jain, 2010). A tumor targeted nanodrug consisting of SPIONs (MN-EPPT-siBIRC5), which is designed to specifically carry siRNA to human breast tumors, binds the tumor-specific antigen uMUC-1 found on over 90% of human breast adenocarcinomas, translating into a significant decrease in tumor growth rate (Kumar et al., 2010). This approach enables simultaneous targeted delivery of siRNA to tumors and the imaging of the delivery process (Jain, 2010; Kumar et al., 2010).

Gold nanomaterials for thermal ablation

Noninvasive radiowave thermal ablation of cancer cells is feasible when facilitated by gold nanoparticles (Cardinal et al., 2008). CYT-6091, a pegylated colloidal gold nanoparticle containing tumor necrosis factor-α bound to its surface, has been extensively investigated as an adjuvant and has been shown to enhance thermal therapies (Shenoi et al., 2009). Nanorods coated with cetyltrimethylammonium bromide (a cationic surfactant used in nanorod synthesis) are internalized quickly into cancer cells by a nonspecific uptake pathway, whereas the removal of cetyltrimethylammonium bromide from nanorods functionalized with folate results in their accumulation on the cell surface over the same time interval (Huff et al., 2007). Thus the nanorods render the tumor cells highly susceptible to photothermal damage when irradiated at the nanorods' longitudinal plasmon resonance (Huff et al., 2007; Jain, 2010).

Magnetic nanoparticles for thermal ablation of tumors

Magnetic nanoparticles are promising tools for minimally invasive elimination of small tumors in the breast using magnetically induced heating (Jain, 2005; Jain, 2010). The approach complies with the increasing demand for breast-conserving therapies and has the advantage of offering a selective and refined tuning of the degree of energy deposition, allowing an adequate temperature control at the target (Hilger et al., 2005). Anti-human epidermal growth factor receptor 2 (anti-HER2) antibody can induce antitumor responses and can be used in delivering drugs to HER2-overexpressing cancer (Jain, 2010). Anti-HER2 immunoliposomes containing magnetite nanoparticles, which act as tumor-targeting vehicles, have been used to combine anti-HER2 antibody therapy with hyperthermia (Ito et al., 2004). Magnetorelaxometry can also be used to monitor the accumulation of magnetic nanoparticles before cancer therapy, with magnetic heating being an important precondition for treatment success (Richter et al., 2010). Although nanoparticle-mediated thermal therapy is a promising treatment of cancers, challenges posed by this form of hyperthermia include the nontarget biodistribution of nanoparticles in the reticuloendothelial system when administered systemically, the inability to visualize or quantify the global concentration and spatial distribution of these particles within tumors, the lack of standardized thermal modeling as well as algorithms for determining dose, and the concerns regarding their biocompatibility (Krishnan et al., 2010; Jain, 2010).

Targeted delivery of thermosensitive affibody-conjugated liposomes for cancer

Thermosensitive liposomes have been used as vehicles for the delivery and release of drugs to tumors (Matsumura et al., 2004a; Jain, 2010). To improve the targeting efficacy for breast cancer treatment, a HER2-specific affibody molecule was conjugated to the surface of thermosensitive small unilamellar liposomes measuring 80-100 nm, referred to as "Affisomes," to study the effects of this modification on physical characteristics and the stability of the resulting preparation (Puri et al., 2008). Affisomes released calcein, a water-soluble fluorescent probe, in a temperature-dependent manner, with optimal leakage (90%-100%) at 410°C (Puri et al., 2008). Affisomes are therefore promising candidates for targeted thermotherapy of breast cancer (Jain, 2010).

Role of nanotechnology in personalized therapy of cancer

Personalized management is usually based on pharmacogenetic, pharmacogenomic, pharmacoproteomic and pharmacometabolic information, but other individual variations in patients and environmental factors are also taken into consideration (Jain, 2005; Jain, 2010). Personalization of cancer therapies is based on a better understanding of the disease at the molecular level, and nanotechnology will play an important role in this area (Jain, 2005). With so many nanotechnologies available for drug delivery, it is recommended that computational mathematical tools be used to predict which nanovectors, surface modifications, therapeutic agents and penetration enhancers to use for a multistage drug-delivery strategy that would enable efficient localized delivery of chemotherapeutic drugs and lead to significant improvements in therapy efficacy as well as reduced systemic toxicity, optimizing personalized oncology (Sakamoto et al., 2007; Jain 2010).

Nanobiotechnology in Cancer Treatment

Nanotechnology-based drugs for cancer

Approximately 150 drugs in development for cancer are based on nanotechnology, of which some are already

Table I. *Approved anticancer drugs using nanocarriers*

Trade name/compound	Manufacturer	Nanocarrier
Abraxane/paclitaxel	Abraxis Biosciences	Albumin-bound paclitaxel
Bexxar/anti-CD20 conjugated to iodine-131	Corixa/ GlaxoSmithKline	Radio-immunoconjugate
DaunoXome/ daunorubicin	Diatos (available in France)	Liposome
Doxil/Caelyx/ doxorubicin	Ortho Biotech	Liposome
Myoset/doxorubicin	Cephalon (available in Europe)	Nonpegylated liposome
Oncaspar/PEG-L-asparaginase	Enzon	Polymer-protein conjugate
Ontak/IL-2 fused to diphtheria toxin	Eisai Inc	Immunotoxic fusion protein
SMANCS/zinostatin	Yamanouchi Pharma	Polymer-protein conjugate
Zevalin/anti-CD20 conjuated to yttrium-90	Cell Therapeutics Inc.	Radio-immunoconjugate
Zoladex/goserelin acetate	AstraZeneca	Polymer rods

PEG, Polyethylene glycol; IL-2, interleukin-2; SMANCS, styrene maleic anhydride Neocarzinostatin. This table was adapted and summarized from Jain, 2005 and Jain, 2010.

approved, as shown in Table I, and the rest are in various stages of development (Jain, 2005; Jain, 2007; Jain, 2010).

Current clinical trials using nanobiotechnology for cancer

Table II shows clinical trial phases of anticancer drugs based on nanobiotechnology. In addtition, recent reviews are available (Carter et al, 2008; Ducry et al, 2010; Heidel et al., 2011). For example, SGN-35 (Seattle Genetics) is being investigated in several Phase II clinical trials, and trastuzumab-DM1 (Genentech) is currently in a Phase III clinical trial (Heidel et al., 2011).

Combination of diagnostics with therapeutics

Theranostics is the new field focused on simultaneous diagnosis and treatment of a pathologic condition (Tassinari et al., 2008). Biocompatible nanoparticles are currently under development as cancer theranostic agents which would allow non-invasive diagnosis and precise cancer therapy for accelerating treatment, reducing side-effects of treatment, and improving cancer cure rates in the nearer future (Santra et al., 2009). Dendrimers can be used as advanced contrast agents for imaging techniques such as MRI and can be targeted specifically to cancer cells and also be used to deliver a variety of cancer therapies to improve their safety and efficacy (Jain, 2010). For example, applications of dendrimers in photodynamic therapy, boron neutron capture therapy and gene therapy for cancer are being investigated (Moghimi et al., 2005).

Clinical Application of Nanotechnology for Cancer

Nanoparticle/Nanoscaled formulations of small molecules

Small-molecule drugs often are extremely effective at killing cancer cells they reach, but their small size leads to rapid clearance from circulation and, consequently, significant uptake by non-cancer cells with concomitant side effects that are, at best, undesirable and, at worst, prohibitive of use (Heidel et al., 2011).

Doxil® is one of several nanoparticle formulations of doxorubicin that have been investigated clinically (Gabizon et al., 1994; Matsumura et al., 2004b; Heidel et al., 2011). As expected, incorporation of doxorubicin within these liposomal or micellar formulations significantly alters the drug pharmacokinetics (PK) (Matsumura et al., 2004b; Heidel et al., 2011). With respect to circulation half-life ($t_{1/2}$), while free doxorubicin alone has a $t_{1/2}$ of less than an hour (Gabizon et al., 1994), the micellar formulations extended the plasma half-life by approximately three-fold (Danson et al., 2004; Schmidt et al., 2009), while the liposomal formulations extended it further by more than an additional ten-fold (Gabizon et al., 1994; Mross et al., 2004; Matsumura et al., 2004b; Sutton et al., 2007) (Table III). It is difficult to quantitatively compare these half-life numbers given the differing models use to generate

Table II. *Clinical trials of anticancer drugs using nanocarriers*

Trial stage	Compound	Nanocarrier	References
Phase I	CPX-1 irinotecan	Liposome	Batist et al., 2009
Phase I	MCC465 doxorubicin	mAb-liposome	Matsumura et al., 2004a
Phase II	NC-6004 cisplatin	Micelle	Matsumura et al., 2008
Phase II/III	PK1 doxorubicin	HPMA copolymer	Seymour et al., 2009
Phase III	SP 1049C doxorubicin	Micelle	Valle et al., 2010

mAb, monoclonal antibody; HPMA, N-(2-hydroxypropyl)methacrylamide.

Table III. *Pharmacokinetic (Plasma Half-Life, Clearance Rate) data for doxorubicin and its nanoparticle formulation*

Formulation	Description	Plasma half-life	Clearance Rate	References
Free doxorubicin		$t_{1/2,\alpha}$ = 0.07 h, $t_{1/2,\beta}$ = 9.6 h[a]	14.4±5.6 mL/(min·kg)	Gabizon et al., 2003; Matsumura et al., 2004b
SP1049C	Micelle, Pluronic	$t_{1/2,\alpha}$ = 0.11h, $t_{1/2,\beta}$ = 2.83h, $t_{1/2,\gamma}$ = 48.8 h	12.6 mL/(min·kg)	Schmidt et al., 2009; Matsumura et al., 2004b
NK911	Micelle, PEG, poly(aspartic acid)	$t_{1/2,\alpha}$ = 0.08-0.13h, $t_{1/2,\beta}$ = 1.6-4.7h, $t_{1/2,\gamma}$ = 29.4-241.4h	6.7±1.1 mL/(min·kg)	Gabizon et al., 1994 Matsumura et al., 2004b
Doxil®	PEGylated liposome	$t_{1/2,\alpha}$ = 2.3h, $t_{1/2,\beta}$ = 45.6 h[a]	0.02 mL/(min·kg)	Gabizon et al., 2003; Matsumura et al., 2004b
Myocet®	nonPEGylated liposome	$t_{1/2}$ =50.95 h[b]	1.216 mL/(min·kg)[c]	Danson et al., 2004; Mross et al., 2004

[a]Data is average of that presented for 25 and 50 mg/m^2 dose levels in ref. (Gabizon et al., 1994)
[b]Data is median presented in Table II of ref. (Mross et al., 2004)
[c]Data is median presented in Table I of ref. (Batist et al., 2007) (3.05l/(h·m^2)), converted to units of mL/(min·kg) using values of 70 kg and 1.6 m^2 .
This table is a mainly adapted and supplemented version from the literature (Gabizon et al., 1994; Matsumura et al., 2004b; Mross et al., 2004; Sutton et al., 2007; Heidel et al., 2011) and reorganized.

them, however, so evaluation of additional PK parameters, such as clearance rate, is instructive (Heidel et al., 2011). These results further illustrate the strong impact all of these formulations have on doxorubicin PK and also indicate differences between the micellar and liposomal approaches (Gabizon et al., 1994; Mross et al., 2004; Matsumura et al., 2004b; Sutton et al., 2007; Heidel et al., 2011). For the two micelle-containing formulations, SP1049C (12.6 mL/(min·kg)) has a similar clearance rate to free doxorubicin (14.4±5.6 mL/(min·kg)), and NK911 (6.7±1.1 mL/(min·kg)) reduces the clearance rate only minimally (approximately two-fold) (Matsumura et al., 2004b). These results are consistent with the hypothesis that these micelles may disassemble shortly after administration (Heidel et al., 2011). By contrast, Myocet® (2.57 mL/(min·kg)) reduces the clearance rate by nearly six-fold, and Doxil® (0.02 mL/(min·kg)) has a nearly one-thousand-fold reduced clearance rate (Matsumura et al., 2004b; Mross et al., 2004). These liposomal results suggest that PEGylation plays a key role in reduced clearance of these nanoparticles (Heidel et al., 2011). Nanoparticle formulation of doxorubicin can significantly alter the PK properties of the drug as well as its biodistribution, safety, and efficacy (Sutton et al., 2007; Heidel et al., 2011). Significantly higher drug levels in tumor tissue have been observed with Doxil® than free doxorubicin in multiple cancer models (Maruyama et al., 1994; Siegal et al., 1995). Just as importantly, Doxil® has shown the ability to clinically reduce cardiotoxicity, a hallmark of free doxorubicin treatment (Batist, 2007; Rahman et al, 2007; Heidel et al., 2011). For non-PEGylated liposomes (such as Myocet®), the cardiac-sparing effect is believed to occur because these liposomes generally extravasate in areas that lack tight junctions, found in the vessels that supply the myocardium (Rahman et al, 2007). For PEGylated liposomes, the blunted peak plasma levels of free drug combined with the presumed biounavailability of liposome-entrapped drug circulating through the myocardium are hypothesized for the reduced cardiotoxicity (Rahman et al., 2007; Heidel et al., 2011). Because of their reduced cardiotoxicity, liposomal formulations of doxorubicin (unlike free doxorubicin) can also be used in combination with other cardiotoxic drugs, such as docetaxel and trastuzumab (Chia et al., 2006), allowing for clinical exploration of additional potential therapeutic options.

Conclusions

Nanotechnology has already improved the way disease, particularly cancer, is diagnosed, treated and monitored while reducing toxic side effects associated with previous cancer therapy and increasing efficacy, facilitating the development of personalized management of cancer. Applications of nanotechnology in cancer therapy includes detection of cancer cells, delivery of chemotherapeutic agents and monitoring of treatment response. A fundamental, widespread understanding of new nanotechnology will lead to the more rational design of optimized nanoparticles with improved selectivity, efficacy and safety in the clinical oncology. However, there still remain many challenges to be resolved prior to widespread use of nanotechnology in the clinical practice of oncology, pharmacokinetic studies and toxicology data of new nanodrugs are very limited, still being investigated. As nanotechnologies develop

with a promising future through the advancement of better cancer drug delivery system, toxic side effects of nanodrugs will decrease, improving patients'quality of life and increasing their survival rate in the near future.

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