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Review Article

Current Trends of Nanotechnology for Cancer Therapy

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ABSTRACT: Nanoparticulate technology is of particular use in developing a new generation of more effective cancer therapies capable of overcoming many biological, biophysical and biomedical barriers that the body stages against a standard intervention. Targeted delivery of drug molecules to tumor tissue is one of the most interesting and challenging endeavors faced in pharmaceutical field, due to the critical and pharmacokinetically specific environment that exists in tumor. Over these years, cancer targeting treatment has been greatly improved by new tools and approaches based on nanotechnology. Nanoparticles show much promise in cancer therapy by selectively gaining access to tumor due to their small size and modifiability. In this review, nonmaterial and biomarkers of cancer, general principle of drug targeting to cancer, intracellular mechanisms, nanoparticles based formulation in market, several recent applications in medicine as diagnostic and therapeutic are discussed. The review's basic approach is: the defining features of cancer nanotechnology are embedded in their breakthrough potential for design and development of nanoparticle based drugs.

KEYWORDS: Nanotechnology; Cancer; Nanomedicine; Biomarker

Introduction

Cancer occurs at a molecular level when multiple subsets of genes undergo genetic alterations, either activation of oncogenes or inactivation of tumor suppressor genes. Then malignant proliferation of cancer cells, tissue infiltration and dysfunction of organs will appear (Sarkar et al., 2007). Tumor tissues are characterized with active angiogenesis and high vascular density which keep blood supply for their growth, but with a defective vascular architecture. Combined with poor lymphatic drainage, they contribute to what is known as the enhanced permeation and retention (EPR) effect (Byrne et al., 2008; Iyer et al., 2006). With the development of nanotechnology, the integration of nonmaterial into cancer therapeutics is one of the rapidly advancing fields. It can revolutionize the treatment of cancer. Nanotechnology is the creation and utilization of materials, devices, and systems through the control of matter on the nanometer scale (Jain 2005). Nanocarrier systems can be designed to interact with target cells and tissues or respond to stimuli in well-controlled ways to induce desired physiological responses. They represent new directions for more effective diagnosis and therapy of cancer (G. Linazasoro 2008).

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What is cancer nanotechnology?

Nanotechnology is a "disruptive technology" which drives a new generation of cancer preventive, diagnostic, and therapeutic products, resulting in dramatically improved cancer outcomes. Nanoparticle drug delivery using biodegradable polymers is expected to provide a more efficient way to overcome some of these problems. The pharmacological properties of a polymer-drug conjugate can be manipulated by changing the physical and chemical properties of the drugs based on nanoscale (Fig. 1) (Piotr Grodzinski. 2010). For example, an insoluble drug can be made water

soluble by introducing solubilizing moieties into the polymer, thereby improving its viability and biodegradability.

Formal definitions of nanotechnological devices typically feature the requirements that the device itself or its essential components be man-made, and in the 1–100 nm range in at least one dimension. Cancer-related examples of nanotechnologies include injectable drug delivery nanovectors such as liposome for the therapy of breast cancer (Park J. W. 2002); biologically targeted, nanosized magnetic resonance imaging (MRI) contrast agents for intraoperative imaging in the context of neuro-oncological interventions (Kircher M. F et al., 2003; Neuwalt E. A. 2004) and novel nanoparticle-based methods for high-specificity detection of DNA and protein (Nam J. M. et al., 2004).

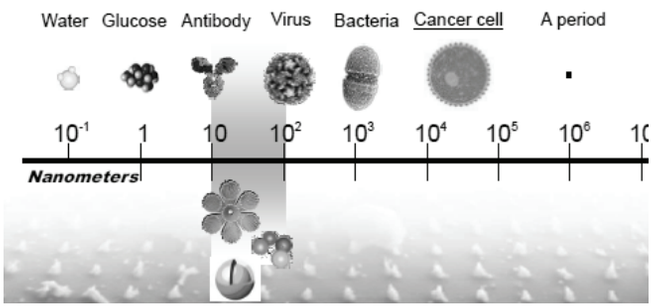

Fig. 1 Different size range of materials on nanoscale.

George Whitesides (Whitesides G. M. 2003) places less stringent limitations on the exact dimensions, and defines the 'right' size in nanobiotechnology in an operational fashion, with respect to addressable unmet needs in biology. Robert Langer and colleagues (La Van, D. A. et al., 2003) argue similarly, in the context of drug-delivery applications in cancer through molecular tumor imaging, early detection, molecular diagnosis, targeted therapy, and cancer bioinformatics (Fig. 2) (Shuming Nie et al., 2007).

Nanomaterials for Cancer Therapy

Nanoparticles used for anticancer drug delivery can be made from a variety of materials, including polymers, dendrimers, liposomes, viruses, carbon nanotubes, and metals such as iron oxide and gold (Table 1) (Dilipkumar Pal et al., 2010). So far, almost all the nanoparticle delivery systems which have been approved by the FDA or are currently in clinic trials are based on polymers or liposomes (Qiu LY et al., 2006).

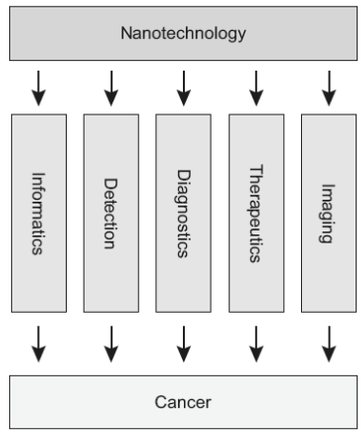

Fig. 2 Schematic diagram showing nanotechnology applications in cancer.

Table 1 Various nanoparticle based delivery systems with their therapeutic and diagnostic uses in cancer therapy.

Nanoparticle based delivery systems	Therapeutic and diagnostic use
Liposomes	Controlled and targeted drug delivery; Targeted gene delivery.
Nanoshells	Tumor targeting
Fullerene based derivatives	As targeting and imaging agent
Carbon nanotube	Drug gene and DNA delivery; Tumor targeting
Dendrimers	Targeted drug delivery
Quantum dots	As targeting and imaging agent
Gold nanoparticles	Targeted delivery and imaging agent
Solid lipid nanoparticle (SLN)	Controlled and targeted drug delivery
Nonowires	As targeting and imaging agent
Paramagnetic nanoparticles	As targeting and imaging agent

Liposomes

Cancer chemotherapeutic drugs and other toxic drugs like amphotericin and hamycin, when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparations. These liposomes can be loaded with drugs either in the aqueous compartment or in the lipid membrane. Usually water soluble drugs are loaded in aqueous compartment and lipid soluble drugs are incorporated in the liposomal membrane (Gregoriadis G et al., 1972). The major limitation of liposome is its rapid degradation and clearance by the liver macrophages (McCormack B et al., 1984), thus reducing the duration of action of the drug it carries. This can be reduced to a certain extent with the advent of stealth liposomes where the liposomes are coated with materials like polyoxyethylene (Illum L et al., 1984) which prevents opsonisation of the liposome and their uptake by macrophages (Senior J et al., 1999). Other ways of prolonging the circulation time of liposomes are incorporation of substances like cholesterol (Kirby C et al., 2003), polyvinylpyrollidone polyacrylamide lipids (Torchilin VP et al., 1994) and high transition temperature phospholipids distearoyl phosphatidylcholine (Forssen EA et al., 2002).

Nanoshells

Nanoshells were developed by West and Halas (West JL et al., 2000) at Rice University as a new modality of targeted therapy. Nanoshells consist of nanoparticles with a core of silica and a coating of thin metallic shell. These can be targeted to desired tissue by using immunological method which is being evaluated for cancer therapy. Hirsh *et al* (Hirsch LR et al., 2003) used nanoshells which are tuned to absorb infra red rays when exposed from a source outside the body to demonstrate the thermo ablative property of nanoshells. The nanoshells when exposed to NIR region of the electromagnetic spectrum get heated and cause destruction of the tissue. This has been studied in both *in vitro* and *in vivo* experiments with HER 2 expressing SK-BR-3 human breast carcinoma cells. The control cells did not lose their viability even after treatment with nanoshells with non specific anti IgG or PEG and NIR ablation (Lowery AR et al., 2006).

Fullerene

Fullerenes (carbon allotrope) also called as “bucky balls” were discovered in 1985 (Thakral S et al., 2006). The buckminster fullerene is the most common form of fullerene measuring about 7 Å in diameter with 60 carbon atoms arranged in a shape known as truncated icosahedrons (Kratschmer W et al., 1990). It resembles a soccer ball with 20 hexagons and 12 pentagons and is highly symmetrical (Taylor R et al., 1990).

Carbon Nanotubes

Carbon nanotubes are cylinders of one several coaxial graphite layers with a diameter in the order of nanometers, and they serve as instructive examples of the Janus-like properties of nanomaterials (Shvedova et al., 2009). They can be classified into two general categories based on their structure: single-walled carbon nanotubes (SWCNTs) with a single cylindrical carbon wall and multiwalled carbon nanotubes (MWCNTs) with multiple walls-cylinders nested within other cylinders (Lacerda et al., 2006). Due to their unique electronic, thermal, and structural characteristics, they can offer a promising approach for gene and drug delivery for cancer therapy (Tanaka et al., 2004). Heating of organs and tissues by placing multifunctional nanomaterials at tumor sites is emerging as an art of tumor treatment by “nanothermal therapy” (Sharma et al., 2009). Carbon nanotubes have become candidates to kill cancer cells via local hyperthermia, due to their thermal conductivity and optical properties.

Dendrimers

Dendrimers are artificial macromolecules with tree-like structures in which the atoms are arranged in many branches and subbranches radiate out from a central core (Morrow et al., 2007). They are synthesized from branched monomer units in a stepwise manner. Thus it is possible to control their molecular properties, such as size, shape, dimension, and polarity, which depend on the branched monomer units (Yang et al., 2009). Based on the specific properties, the dendrimers have shown great promise in the development of anticancer drug delivery systems (Gillies et al., 2005). The well-defined multivalency of

dendrimers are widely exploited for covalent attachment of special targeting moieties, such as sugar (Bhadra et al., 2005), folic acid (Licciardi et al., 2006), antibody (Patri et al., 2004), biotin (Yang et al., 2009) and epidermal growth factors (Hussain et al., 2004) to achieve active targeting drugs to tumor tissues. In vitro studies indicated the DNA-linked dendrimer clusters could specifically bind to KB cells and may be used as imaging agents and therapeutics for cancer therapy (Choi et al., 2005).

Quantum Dots

Quantum dots are inorganic fluorescent semiconductor nanoparticels composed of 10–50 atoms with a diameter ranging from 2 to 10 nm (Cai et al., 2007). Their sizes and shapes which determine their absorption and emission properties can be controlled precisely (Morrow et al., 2007). They are widely studied for optical image application in living systems and are stable for months without degradation and alteration (Cai et al., 2007). Targeted ligands have been attached to QDs in order to achieve specific targeting for tumor cell labeling (Kim et al., 2007). Thus, they are assured to be chosen as long-term, high-sensitivity and multicontrast imaging agents applied for the detection and diagnosis of cancer in vivo (Morrow et al., 2007). Klein and coworkers have developed functionalized silicon quantum dots (SiQDs) to serve as self-tracking transfection tool for ABCB1 siRNA (Klein et al., 2009). Li et al. investigated glutathione-mediated release of functional plasmid DNA from positively charged CdTe quantum dots, which suggested potential applications of these QDs in selective unpacking of payload in living cells in a visible manner (Li et al., 2008).

Gold Nanoparticles

Colloidal gold nanoparticles are another attractive platform for cancer diagnosis and therapy (Paciotti GF et al., 2004). Gold nanoparticles have been used as contrast agents in vitro based on their ability to scatter visible light. Sokolov et al. successfully used gold nanoparticles conjugated to EGFR antibodies to label cervical biopsies for identification of precancerous lesions (Sokolov K et al., 2003). Photoacoustic tomography has been used to image gold nanoparticles to a depth of 6 cm in experiments using gelatin phantoms (Copland JA et al., 2004). In a subcutaneous model of colon cancer, it was demonstrated that systemically delivered gold nanoparticles (size, approximately 33 nm) conjugated to tumor necrosis factor (TNF) accumulated in tumors (Paciotti GF et al., 2004).

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles hold significant promise in cancer treatment. They are particles of submicron size (50 to 1000 nm) made from lipids that remain in a solid state at room as well as body temperature. Various anticancer agents like doxorubicin, daunorubicin, idarubicin, paclitaxel, camptothesins, etoposide, etc have been encapsulated using this nanotechnological approach. Several obstacles frequently encountered with anticancer agents, such as a high incidence of drug resistant tumor cells can be partially overcome by delivering them using solid lipid nanoparticles (Wong HL et al., 2007).

Nanowires

Nanowires are glowing silica wires in nanoscale, wrapped around single strand of human hairs. They are about five times smaller than virus and several times stronger than spider silk. Nanowire based arrays have significant impact for early diagnosis of cancer, and cancer treatment. The nanowire-based delivery enables simultaneous detection of multiple analytes such as cancer biomarkers in a single chip, as well as fundamental kinetic studies for bio-molecular reactions (Zheng G et al., 2006). Protein coated nanowires have potential applications in cancer imaging like prostate cancer, breast cancer and ovarian malignancies.

Paramagnetic Nanoparticles

Paramagnetic nanoparticles are being tried for both diagnostic and therapeutic purposes.

Diagnostically, paramagnetic iron oxide nanoparticles are used as contrast agents in magnetic resonance imaging. These have a greater magnetic susceptibility than conventional contrast agents. Targeting of these nanoparticles enables identification of specific organs and tissues

(Cuenca AG et al., 2006). The use of iron oxide in MRI imaging faces limitations like specificity and internalization by macrophages (Peng XH et al., 2008). Paramagnetic nanoparticles conjugated with antibodies to HER-2/*neu* which are expressed on breast cancer cells have been used with MRI to detect breast cancer cells *in vitro* (Artemov D et al., 2003).

Monocrystalline iron oxide nanoparticles (MIONs) have been studied by Knauth *et al* (Knauth M et al., 2001) in magnetic resonance imaging of brain. MIONs help in overcoming the disadvantage of surgically induced contrast enhancement with traditional contrast agents resulting in misinterpretation during intra-operative MR imaging of brain. Magnetic nanoprobes are used for cancer therapy. Iron nanoparticles coated with monoclonal antibodies directed to tumour cells can be made to generate high levels of heat after these accumulate in their target site by means of an alternating magnetic field applied externally. This heat kills the cancer cells selectively which was designed by Triton Biosystems, is about to enter clinical trials for solid tumours in 2009 (Aduro BT Berkeley 2008).

Cancer Disease

Cancer is a leading cause of death worldwide. From a total of 58 million deaths worldwide in 2005, cancer accounts for 7.6 million (or 13%) of all deaths. More than 70% of all cancer deaths in 2005 occurred in low and middle-income countries. Deaths from cancer in the world are projected to continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million dying in 2030. The most frequent cancer types worldwide are (a) among men: lung, stomach, liver, colorectal, oesophagus and prostate; and (b) among women: breast, lung stomach, colorectal and cervical (Pan American Health Organisation, WHO 2006).

Biomarkers of Cancer

Biomarkers include altered or mutant genes, RNAs, proteins, carbohydrates, lipids, and small metabolite molecules, and their altered expressions that are correlated with a biological behavior or a clinical outcome. Most cancer biomarkers are discovered by molecular profiling studies based on an association or correlation between a molecular signature and cancer behavior. In the cases of both breast and prostate cancer, a deadly step is the appearance of so-called lethal phenotypes, such as bone-metastatic, hormone-independent, and radiation and chemotherapy-resistant phenotypes. It has been hypothesized that each of these aggressive behaviors or phenotypes could be understood and predicted by a defining set of biomarkers (Shuming Nie et al., 2007). Biomarkers have tremendous therapeutic impact in clinical oncology, especially if the biomarker is detected before clinical symptoms or enable real-time monitoring of drug response. Protein signatures in cancer provide valuable information that may be an aid to more effective diagnosis, prognosis, and response to therapy. The recent progress of proteomics has opened new avenues for cancer-related biomarker discovery. Advances in proteomics are contributing to the understanding of patho-physiology of neoplasia, cancer diagnosis, and anticancer drug discovery. Continued refinement of techniques and methods to determine the abundance and status of proteins holds great promise for the future study of cancer and the development of cancer therapies (Cho. 2006). Current cancer biomarkers in use are shown in Table 2a and 2b (Young-Eun Choi et al., 2010).

Early diagnosis of cancer is difficult because of the lack of specific symptoms in early disease and the limited understanding of etiology and oncogenesis. For example, blood tumor markers for breast cancer such as cancer antigen (CA) 15-3 are useless for early detection because of low sensitivity (Cho. 2007). More than 98% of cervical cancer is related to human papilloma virus (HPV) infection. The identification and functional verification of host proteins associated with HPV E6 and E7 oncoproteins may provide useful information for the understanding of cervical carcinogenesis and the development of cervical cancer-specific markers (Yim et al., 2006). There is a critical need for expedited development of biomarkers and their use to improve diagnosis and treatment for cancer (Alok Kumar Singha et al., 2008).

Table 2a Current cancer biomarkers in use.

Cancer	Markers	Characteristics	Typical Sample
Prostate	PSA (Prostate specific antigen), total and free	High sensitivity in all stages; also elevated from some non-cancer causes	Blood
	PSMA (Prostate specific membrane antigen)	Levels tend to increase with age	Blood
Breast	CA 15-3, 27, 29 (Cancer antigen 15-3, 27, 29)	Elevated in benign breast conditions. Either CA 15-3 or CA 27, 29 could be used as marker	Blood
	Estrogen receptors	Overexpressed in hormone-dependent cancer	Tissue
	Progesterone receptors		Tissue
	Her-2/neu	Only 20~30% of patients are positive to Her-2 oncogene that is present in multiple copies	Tissue
Lung (non-small cell)	CEA (Carcinoembryonic antigen)	Used in combination with NSA to increase specificity, used also for colon cancer detection	Blood
Lung (small cell)	NSE (Neuron-specific enolase)	Better sensitivity towards specific types of lung caner	Blood
Bladder	NMP22 (Matritech's nuclear matrix protein), BTA (Bladder tumor antigen)	NMP-22 assays tend to have greater sensitivity than BTA assays	Urine
Pancreatic	BTA	Composed of basement membrane complexes	Urine
	CA 19-9 (Carbohydrate antigen 19-9)	Elevated also in inflammatory bowel disease, sometimes used as colorectal cancer biomarker	Blood
Epithelial ovarian cancer (90 % of all ovarian cancer)	CA 125 (Cancer antigen 125)	High sensitivity in advanced stage; also elevated with endometriosis, some other diseases and benign conditions	Blood
Germ cell cancer of ovaries	CA 72-4 (Cancer antigen 72-4)	No evidence that this biomarker is better than CA-125 but may be useful when used in combination	Blood
	AFP (Alpha-fetoprotein)	Also elevated during pregnancy and liver cancer	Blood

Table 2b Current cancer biomarkers in use (Contd.).

Cancer	Markers	Characteristics	Typical Sample
Multiple myeloma and lymphomas	B2M (Beta-2 microglobulin)	Present in many other conditions, including prostate cancer and renal cell carcinoma.	Blood
	Monoclonal immunoglobulins	Overproduction of an immunoglobulin or antibody, usually detected by protein electrophoresis	Blood, urine
Metastatic melanoma	S100B	Subunit of the S100 protein family	Serum
	TA-90(Tumor-associated glycoprotein	Could be used to monitor patients with high risks of developing the disease	Serum

Table 2b *contd…*

Cancer	Markers	Characteristics	Typical Sample
Thyroid	Thyroglobulin	Principal iodoprotein of the thyroid gland	Serum,
Thyroid medullary carcinoma	Calcitonin	Secreted mainly by parafollicular C cells	Blood, serum
Testicular	hCG (Human chorionic gonadotropin)	May regulate vascular neoformation through vascular endothelial growth factor (VEGF)	Serum
Waldenstrom's macroglobulinemia (WM)	Monoclonal Immunoglobulin M	The larger size and increased concentration of the monoclonal protein leads to serum hyperviscosity, the most distinguishing feature of WM	Blood, urine
Lymphomas	B2M	Present in many other conditions, including prostate cancer and renal cell carcinoma	Serum
Lung (non small cell), epithelial, colorectal, head and neck, pancreatic, or breast	EGFR (Her-1)	Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation	Tissue
Colorectal, lung, breast, pancreatic, and bladder	CEA (Carcinoembryonic antigen)	Subtle posttranslational modifications might create differences between tumor CEA and normal CEA	Serum
T-cell acute lymphoblastic leukemia (T-ALL)	PTK7	Membrane-bound surface protein of whole cells, and can be used to detect circulating tumor cells as targets	Blood

General Principles of Drug Targeting to Cancer

Passive targeting

Passive targeting refers to the accumulation of drug or drug-carrier system at a particular site due to physicochemical or pharmacological factors. Permeability of the tumor vasculature increases to the point where particulate carriers such as nanoparicles can extravasate from blood circulation and localize in the tumor tissue (Maeda H. 2000; Maeda, H. et al., 2001). This occurs because as tumors grow and begin to outstrip the available supply of oxygen and nutrients, they release cytokines and other signaling molecules that recruit new blood vessels to the tumor, a process known as angiogenesis (Folkman J. et al., 1992). Angiogenic blood vessels, unlike the tight blood vessels in most normal tissues, have gaps as large as 600–800 nm between adjacent endothelial cells. Drug carriers in the nanometer size range can extravasate through these gaps into the tumor interstitial space (Jain, R. K. 1998).

Because tumors have impaired lymphatic drainage, the carriers concentrate in the tumor, resulting in higher drug concentration in the tumor tissue (10-fold or higher) than that can be achieved with the same dose of free drug. This is commonly referred to as enhanced permeability and retention, or the EPR effect. Normal tissue vasculatures are lined by tight endothelial cells, thereby preventing nanoparticle drugs from escaping or extravasation, whereas tumor tissue vasculatures are leaking and hyperpermeable allowing preferential accumulation of nanoparticles in the tumor interstitial space (called passive nanoparticle tumor targeting) (Fig. 3) (La Van. Et al., 2003).

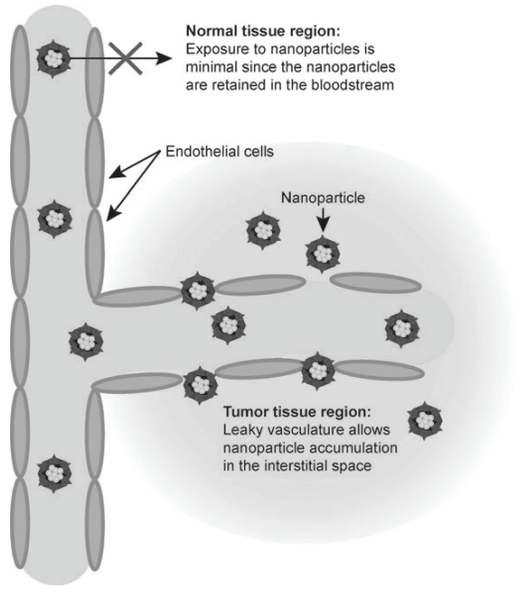

Fig. 3 Schematic diagrams showing enhanced permeability and retention of nanoparticles in tumors.

Active targeting

Active targeting to the tumor can be achieved by molecular recognition of cancer cells either via ligand–receptor or antibody–antigen interactions. Active targeting may also lead to receptormediated cell internalization of drug carrier system. Nanoparticles and other polymer drugconjugates offer numerous opportunities for targeting tumors through surface modifications which allow specific biochemical interactions with the proteins/receptors expressed on target cells (Panyam J. et al., 2003; Minko T. 2004). For active and passive targeting of drug carrier systems, it is essential to avoid their uptake by the reticuloendothelial system (RES) so that they remain in the blood circulation and extravasate in the tumor vasculature. Particles with more hydrophobic surfaces are preferentially taken up by the liver, followed by the spleen and lungs (Gref R. 1994, Gref, R. 1997). Sizes of nanoparticles as well as their surface characteristics are the key parameters that can alter the biodistribution of nanoparticles.

Particles smaller than 100 nm and coated with hydrophilic polymers such as amphiphilic polymeric compounds which are made of polyethylene oxide such as poloxamers, poloxamines, or polyethylene glycol (PEG) are being investigated to avoid their uptake by the RES. To improve the efficacy of targeting cancer chemotherapeutics to the tumor, a combination of passive and active targeting strategy is being investigated where long-circulating drug carriers are conjugated to tumor cell specific antibody or peptides (Vasir, J. K. et al., 2005).

In addition to the above approach, direct intratumoral injection of the carrier system is feasible if the tumor is localized and can be accessed for administration of a carrier system (Sahoo S. K. et al., 2004). The nanoparticle drug is internalized by tumor cells through ligand-receptor interaction. Depending on the design of the cleavable bond, the drug will be released intracellularly on exposure to lysosomal enzymes or lower pH (Fig. 4) (La Van. Et al., 2003).

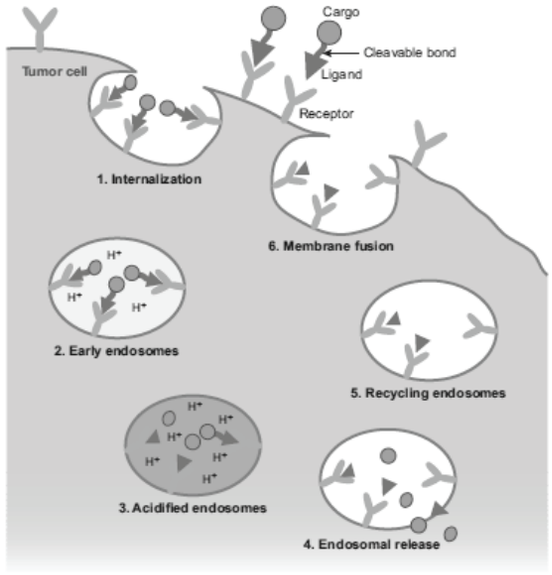

Fig. 4 Nanoparticle drug delivery and targeting using receptor-mediated endocytosis.

Nanoparticle Drugs and its Application

Nanoparticle drugs are designed by encapsulating, covalently attaching or adsorbing therapeutic and diagnostic agents to the nanoparticle. Recently Food and Drug Administration (FDA) approved Abraxane**TM** an albumin -paclitaxel (Taxol**TM**) nanoparticle drug for the breast cancer treatment. Nanoparticle structure (Fig. 5) was designed by linking hydrophobic cancer drug (Taxol) and tumor-targeting ligand to hydrophilic and

biodegradable polymer which delivers 50% higher dose of active agent Taxol**TM** to the targeted tumor areas. Some nanoparticles used for medical application are shown in Table 3 (A. Surendiran. et al., 2009).

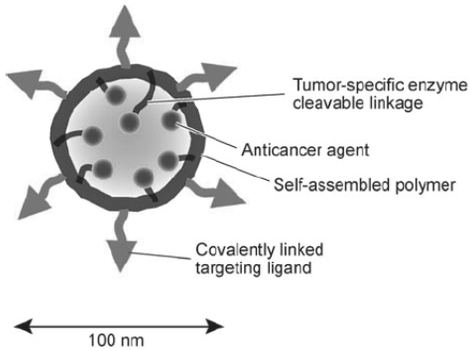

Fig. 5 Nanoparticle containing anticancer agent.

Commercially available Nano Drug Delivery Systems

Despite the challenges which include the huge volume of expenditure involved and the regulatory stages which are mandatory in order to obtain regulatory approval before a drug can get into the market, some nano drug delivery systems have made it to the market. Table: 4a and 4b shows the list of some of nano drug delivery systems in the market (Wagner V et al., 2006).

Future Directions

The first major direction in design and development of nanoparticles are monofunctional, dual functional, tri functional and multiple functional probes. Bioconjugated QDs with both targeting and imaging functions will be useful in targeted tumor imaging and molecular profiling applications. Consequently nanoparticles with three functional groups could be designed for simultaneous imaging and therapy with targeting. The second direction is to study nanoparticle distribution, metabolism, excretion and pharmacodynamics in in vivo animal models. These investigations will be very important in the development and design of nanoparticles for clinical applications in cancer treatment.

Table 3 Some nanoparticles used for medical applications.

Study phase	Product	Description	Use	Manufacturer
Preclinical	MRX 952	Nanoparticle preparation – to encapsulate camptothecin analogues	Tumors	IMA Rx Therapeutics
Preclinical	Targeted Nano Therapeutics (TNT)™ system	TNT with polymer coated iron oxide magnetic particle	Solid tumors	Triton Biosystems
Preclinical	AuroLase™	Gold nanoshell	Head and neck cancer	Nanospectra Biosciences Inc
Preclinical	Dendrimer-Magnevist#	PAMAM dendrimer	MRI imaging agent	Dendritic Nanotechnologies Inc
Phase 1	VivaGel®	Dendrimer based microbicide gel	HIV prevention	Starpharma Pty Ltd
Phase 1	INGN 401	Nanoparticle formulation of tumour suppression gene FUS1	Lung cancer	Introgen Therapeutics Inc
Phase 1&2	Cyclosert-Camptothecin–IT 101	β-Cylcodextrin polymer drug delivery system	Solid tumours	Calando Pharmaceuticals
Phase 2	VivaGel®	Dendrimer based microbicide gel	HSV prevention	Starpharma Pty Ltd
Phase 2	MRX 815	Nanobubble technology	Treatment of intravascular clot	IMA Rx Therapeutics

Table 3 *Contd…*

Study phase	Product	Description	Use	Manufacturer
Phase 3	Combidex® / Ferumoxtran10	Iron oxide nanoparticle	MRI contrast agent	AMAG Pharmaceuticals
Marketed	Abraxane®	Albumin bound taxane particles	Non small cell lung cancer	Abraxis Oncology
Marketed	AmBisome®	Liposomal preparation of amphotericin B	Fungal infection	Astellas Pharma US
Marketed	Doxil®	Liposomal doxorubicin	Ovarian tumour	Ortho Biotech

#Available at Nanotechnology Characterization Laboratory Webpage: *http://ncl.cancer.gov/*

Table 4a Nano drug delivery systems in the market.

Type of nanostructure	Trade name	Active ingredient	Indication	Company
Polymeric nanoparticles	Adagen	Adenosine deaminase	Adenosine deaminase (ADA) enzyme deficiency	Enzon Pharmaceuticals Inc., Bridgewater, NJ, USA
	Onscaspar	L-asparaginase	Acute lymphoblastic leukaemia	Enzon Pharmaceuticals Inc., NJ, USA
	Copaxone	Glatiramer Acetate	Relapsing-remitting multiple sclerosis	Teva Pharmaceuticals, Tikva, Isreal
	Macugen	Pegaptanib Sodium	All types of neovascular age- related macular degeneration	Nektar Therapeutics, San Carlos, CA, USA; OSI Pharmaceuticals, Melville, NY, USA
	Pegasys	Pegylated interferon alfa-2a	Hepatitis C	Nektar Therapeutics, CA, USA
	Neulasta	Pegfilgrastim	Neutopenia	Nektar Therapeutics, CA, USA; Amgen Inc, Thousand Oaks, CA, USA
	PEG-INTRON	Peginterferon alfa-2b	Hepatitis C	Nektar therapeutics, CA, USA
	Somavert	Pegvisomant	Acromegaly	Nektar therapeutics, CA, USA
Liposomes	Abelcet	Amphotericn B	Fungal infections	Enzon Pharmaceuticals Inc., NJ, USA
	Depocyt	Cytarabine	Lymphomatous meningitis	Enzon Pharmaceuticals Inc., NJ, USA
Liposomes	AmBisome	Amphotericn B	Fungal infections	Gilead Sciences Inc., Foster City, CA, USA
	Daunoxome	Daunorubicin	Kaposi's sarcoma	Gilead Sciences Inc., CA, USA
	Myocet	Doxorubicin	Advanced breast cancer	Zeneus/Cephalon, Inc., Frazer, PA, USA
	Epaxal	Inactivated Hepatitis A virus	Hepatitis A	Berna Biotech, Bern, Switzerland
	Inflexal V	Inactivated influenza surface antigen	Influenza	Berna Biotech, Bern, Switzerland
	DepoDur	Morphine	Analgesia	EKR Therapeutics, Bedminster, NJ, USA
	Visudyne	Verteporfin	Age-related macular degeneration	QLT Inc., Vancouver, British Colombia, Canada; Norvatis, Basel, Switzerland

Table 4b Nano drug delivery systems in the market (contd.).

Type of nanostructure	Trade name	Active ingredient	Indication	Company
	Doxil	Doxorubicin	Ovarian cancer and Kaposi's sarcoma	Ortho Biotech, Bridgewater, NJ, USA
	Caelyx	Doxorubicin	Ovarian cancer, Kaposi's sarcoma & breast cancer	Schering-Plough, Kenilworth, NJ, USA
	Estrasorb	Estradiol	Menopausal – Hot flushes	Novavax, Rockville, MD, USA
	Survanta	Beractant (bovine lung homogenate)	Respiratory distress syndrome	Abbott Laboratories, IL, USA
Liposomes	Alveofact	Bovactant(bovine lung lavage)	Respiratory distress syndrome	Boehringer Ingelheim GmbH,Ingelheim, Germany
	Curosurf	Poractant alfa (porcine lung homogenate)	Respiratory distress syndrome	Chiesi Farmaceutici SpA, Parma, Italy
Polymeric micelles	Genexol-PM	Paclitaxel	Cancer chemotherapy	Samyang Pharmaceutical, Daejeon City, Korea
Nanocrystalline drugs	Rapamune	Sirolimus	Immunosuppressant	Elan Corporation, Dublin, Ireland; Wyeth Pharmaceutical , Madison, NJ, USA
	Emend	Aprepitant	Antiemetic	Elan Corporation, Dublin, Ireland; Merck and Co., Inc. Whitehouse Station, NJ, USA
	Tricor	fenofibrate	Hyperlipidemia	Elan Corporation, Dublin, Ireland; Abbott Labs, Illinois, USA
	Megace	Megestrol acetate	Anorexia, Cachexia	Elan Corporation, Dublin, Ireland; Par Pharmaceuticals, Woodcliff Lake, NJ, USA
Protein (albumin) nanoparticles	Abraxane	Paclitaxel	Metastatic breast cancer	Abraxis BioScience, Los Angeles, CA, USA;Astra Zeneca, London, UK
Lipid colloidal dispersion	Amphotec	Amphotericin B	Fungal infections	InterMune, Brisbane, CA, USA

Conclusion

Cancer nanotechnology field has the potential to better monitor therapeutic efficacy, provide novel methods for detecting and profiling early stage cancers, and for enabling surgeons to delineate tumor margins and sentinel lymph nodes. Nanomaterials have unique features that are attractive, and can be applied to biosensing. The development of various nanomaterials and nanotechnology has enabled detection of cancer biomarkers with great precision and sensitivity that could not be achieved before. Many studies are being conducted on developing sensing mechanisms that will push down the detection limit as far down as possible. As well, various new biomarkers can be discovered and verified with such sensitive tools. It is therefore highly anticipated that in the near future, nanotechnology shall help to detect cancer at an early

stage and monitor the disease with much greater precision. It must be however noted that these new technologies must be validated critically before applying them for clinical diagnosis. Ultimately, if the nanotechnology researchers can establish methods to detect tumors at a very early stage, that is, before tumors begin to vascularize and metastasize, cancer will become a disease that will become amenable to complete cure via surgical resection.

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