Introduction

The first description of cancer is found in an Egyptian papyrus and dates back to approximately 1600 BC. It was regarded as an incurable disease until the nineteenth century, when surgical removal was made more efficient by improved techniques of anesthesia. After 1960, radiation therapy was being prominently used to control local disease. However, with the passage of time, it was realized that neither surgery nor radiation or the two in combination could adequately control the disease. For treatment to be effective, therapy needed to reach every organ of the body.

Current efforts to cure cancer have been focusing on drugs, biological molecules and immune mediated therapies. The introduction of nitrogen mustard in the 1940s can be considered the origin of anti-neoplastic chemotherapy targeting all tumor cells (Papac et al. 2001). Efforts to fight the disease were intensified after US passed the National Cancer Act in 1971 and President Nixon declared a “war on cancer” (Dunn et al. 2002). Today more than 30 years after, although improved mortality rate of cancer patients has not improved or survival time prolonged as much as was expected, key characteristics and pathways of different tumor have been identified. This knowledge is now used to generate specific tumor therapies either by directly targeting the proteins involved in the neoplastic process or by targeting drugs to the tumor.

Cancer is the result of cell growth regulation gone away. Any cell in the body has the potential to become cancerous, if it receives a series of genetic mutations that result in growth de-regulation. The mutated cell(s) will continue to divide, forming what is called the primary tumor. The tumor may be benign or it may begin to invade surrounding tissues, breaking through basal laminas the natural boundaries of a particular tissue. Certain cells from these tumors may also mutate such that they gain the ability to leave the site of the primary tumor, enter the bloodstream and carried to another tissue or organ, and begin the formation of a new tumor. Tumor cells are also very adept at escaping from the constant patrol of the immune system, which

ABSTRACT

Cancer medically known as malignant neoplasm is a group of different diseases all involving unregulated cell growth due to defects in the genetic makeup of two types of genes, i.e., oncogene, which drive the growth of cancer cells and tumor suppressor genes which prevent cancer from developing. Cancer is detected in a number of ways, including symptoms, screening tests, medical imaging and is usually treated with chemotherapy, radiation therapy and surgery. With the advancement in medical sciences, targeted cancer therapy has got lot of importance which has many benefits, comforts and patient friendly as compared to conventional therapies. This review gives an insight of the various targeted therapies, their role and impact in treatment of various types of cancers. Targeted cancer therapies like monoclonal antibodies, nanoparticle-aptamer bioconjugates, oligopeptide-based, folate-based, AdNectins, microfluidics and nanotechnology approaches have led to deliver target-oriented toxic drugs to specific cancer cells.

Key words: Cancer; Targeted Therapies; Carriers; Nanotechnology
should be able to recognize them as aberrant. For example, tumor cells often shed surface antigens that might identify them as abnormal. It is the combination of all these aspects that makes cancer such a difficult disease to cure.

In recent times, researchers from worldwide have been exploring controlled-release or targeted-delivery options for cancer treatment. These act by locally concentrating the drugs for sustained periods of time, thereby reducing systemic toxicity (Mathiowitz et al. 1999). Targeted therapy encompasses a wide variety of direct and indirect approaches. Direct approaches target tumor antigens to alter their signaling either by monoclonal antibodies (MoAbs) or by small molecule drugs that interfere with these target proteins. Indirect approaches rely on tumor antigens expressed on the cell surface that serve as target devices for ligands containing different kinds of effectors molecules. In these approaches, drugs can actively target tumors using tumor-specific MoAbs or peptide ligands binding to receptors that are present on tumor cells. In addition to active targeting, tumors can also be passively targeted by macromolecules through the enhanced permeability and retention effects attributed to the hyper permeable angiogenic tumor vasculature and the lack of effective tumor lymphatic drainage.

Present review provides an overview of current site and tissue specific strategies for understanding the targeted cancer therapy and exploring more efficacious and novel approaches with clinical promise.

Challenges in cancer therapy: rationale for targeted cancer therapy

Chemotherapy has remained an integral component of treatment for most cancers. Despite the last 30 years of efforts on oncology drug discovery, conventional chemotherapeutic agents still exhibit poor specificity in reaching tumor tissue and are often restricted by dose-limiting toxicity. The combination of controlled release technology and targeted drug delivery may provide a more efficient and less harmful solution to overcome the limitations of conventional chemotherapy. Recent interest has been focused on developing nanoscale delivery vehicles capable of controlling the release of chemotherapeutic agents directly inside cancer cells (Bisht et al. 2008, Patel et al. 2011, Cao et al. 2011, Paraskar et al. 2012). Controlled release occurs when a natural or synthetic polymer is combined with a drug in such a way that the drug is encapsulated within the polymer system for subsequent release in a predetermined manner. Polymeric drug delivery vehicles that are designed as particles can range in size from 50nm to over 10μm and can release encapsulated drugs through surface, bulk erosion, diffusion or swelling followed by diffusion in a time - or condition-dependent manner. The release of the active agent may be constant over a long period or it may be triggered by the environment or other external events (Farokhzad et al. 2006). In general, controlled-release polymer systems can provide drug levels in optimum range over a longer period of time, thus increasing the efficacy of the drug and maximizing patient compliance. Besides, other advantages include maintenance of drug levels within a desired range, need for fewer administrations, optimal use of the drug, and increased patient compliance.

Targeted therapy

Cancer antigens can be identified and targeted at molecular level which has opened new possibilities for the development of effective antibodies therapy and ligand-targeted therapy for cancer patients. Ligand-targeted therapy is a successful tool for controlling the selective toxicity of anticancer therapeutics. The molecular pathways most often targeted in the treatment of solid tumors (e.g., breast, lung, and colorectal cancers) are the epidermal growth factor receptor (EGFR, also known as HER1), vascular endothelial growth factor (VEGF), and HER2/neu (Sledge et al. 2010). Such pathways can be inhibited at multiple levels; by binding and neutralizing ligands (i.e. molecules that bind to specific receptor sites on cells); by occupying receptor-binding sites (thereby preventing ligand binding); by blocking receptor signaling within the cancer cell; or by interfering with downstream intra-cellular molecules. Monoclonal antibodies are usually water soluble and having large MW (~150,000 Da) target extracellular components of these pathways, such as ligands and receptor-binding domains. In contrast, small molecule inhibitors (MW of approximately 500 Da) enter cells, thereby blocking receptor signaling and interfering with downstream intracellular molecules (Langer et al. 2004).
EGFR present in multiple tumor types contributes to cancer cell proliferation, invasion and migration (Mendelsohn and Baselga, 2006). EGFR is present in normal epithelial tissues (i.e., skin and mucosa) and its inhibition can lead to significant dermatologic and gastrointestinal toxicities. In many cases the development of rash indicates that the treatment may be working (Mohamed et al. 2005, Park et al. 2004, Agero et al. 2006) and in severe cases, dermatologic toxicity may require discontinuation of the EGFR inhibitor and implementation of measures such as topical or systemic antibiotics, topical retinoids or topical steroids (Agero et al. 2006). Fifty percent of patients taking EGFR inhibitors develop diarrhea but this toxicity is self-limiting and responds to symptomatic treatment.

In some instances, targeted therapy has led to tailored therapy. Trastuzumab (Herceptin) is a monoclonal antibody directed against HER2/neu, a molecular target related to EGFR that is over expressed in approximately 25% of patients with breast cancer (Slamon et al. 1987). Trastuzumab is ineffective in the 75% of patients with breast cancers that do not over express HER2/neu, it is used where HER2/neu is over expressed in tumor tissue (Wang et al. 2005; Romond et al. 2005; Piccart-Gebhart et al. 2005; Schuetz et al. 2011, Lin et al. 2012). Moreover targeting of EGFR is most effective in patients with non-small cell lung cancer that are highly dependent on the EGFR signaling pathway (Scaglioni et al. 2004). This trait is most likely to occur in nonsmoking Asian females with bronchiole alveolar-type tumors (Calvo et al. 2006). A regimen of trastuzumab being used in combination with other targeted therapies in HER2-positive metastatic breast cancer seems promising (Pegram and Liao, 2012).

**Active versus passive cancer targeting**

Active and passive targeting strategies rely on delivering drug-encapsulated nanoparticles (NP) to cancerous tissue. Active targeting approach uses the unique property of the tumor microenvironment most notably (i) leaky tumor vasculature, which is highly permeable to macromolecules relative to normal tissue, and (ii) a dysfunctional lymphatic drainage system, which results in enhanced fluid retention in the tumor interstitial space. As a result the concentration of polymeric NP and macromolecular assemblies found in tumor tissues can be up to 100 times higher than those in normal tissue (Matsumura and Maeda 1986). The tumor-specific deposition also known as the enhanced permeability and retention (EPR) effect occurs as NP extravasate out of tumor microvasculature, leading to an accumulation of drugs in the tumor interstitium (Danhier et al. 2010). The extent of NP extravasation depends on the size of open inter-endothelial gap junctions and trans-endothelial channels. The pore cut off size of these transport pathways has been reported between 400-600 nm and extravasation of liposomes into tumors in vivo suggests a cutoff size in the range of 400 nm (Yuan et al. 1995). In general, particles with diameters less than 200 nm are the most effective for extravasating tumor microvasculature (Kong et al. 2000).

Active targeting by and large is thus achieved by both local and systemic administration of delivering drug encapsulated NP to uniquely identified sites targeting molecules conjugated on the particle surface that can recognize and bind to specific ligands that are unique to cancer cells while having minimal undesired affect elsewhere. This approach is particularly useful for primary tumors that have not yet metastasized. For example, suicide targeted gene delivery has been demonstrated to be effective in killing prostate cancer but not healthy muscle cells in xenograft mouse models of prostate cancer (Anderson et al. 2004; Ferrari et al. 2005). For metastatic cancers, the location, abundance and size of tumor within the body limits its visualization or accessibility thus making local delivery approaches impractical. In this case, the drug delivery vehicle would be administered systemically. In comparison passive targeting uses pharmacokinetic manipulation and NP size reduction. However, biggest limitation of passive tumor targeting is the inability to achieve a sufficiently high level of drug concentration at the tumor site resulting in low therapeutic efficacy and eliciting undesirable systemic adverse effects (Brigger et al. 2002, Ferrari et al. 2005).

**Carriers for Targeted Therapy**

Active targeting can be achieved by the functionalization of NP with ligands such as antibodies, peptides, nucleic acid aptamers,
carbohydrates and small molecules. As discussed in the next section of this review, some of these therapeutic conjugates are now under clinical development or in clinical practice today. However, the success has been largely limited to ligand–drug conjugates (Vineesh et al. 2012) and attempts have been made to enhance these systems by encapsulating the therapeutic agents in NP. Several classes of materials have been developed for targeted NP including biodegradable polymers, dendrimers, nanoshells, nucleic-acid-based NP and liposomes.

Biodegradable polymer NPs have been extensively investigated (Feng et al. 2004, Sajja et al. 2009). Polymeric NPs typically have a prolonged systemic circulating half-life by grafting, conjugating or adsorbing sterically amphiphilic polymers such as polyethylene glycol (PEG) to the particle surface (Gref et al. 2000, Owens et al. 2006). Polymeric NP can be formulated to encapsulate hydrophilic or hydrophobic small drug molecules and macromolecules such as proteins and nucleic acids (Tobio et al. 1998, Perez et al. 2001). These NPs can be used to release the encapsulated drugs at a controlled rate via surface or bulk erosion, diffusion or swelling followed by diffusion in a time- or condition-dependent manner. The rate of drug release can be controlled by modification of the polymer side chain, development of novel polymers or synthesis of copolymers (Lu et al. 2011, Zhang et al. 2012). Targeted therapeutic approaches significantly benefit from the combination of targeted delivery with controlled release technology (Zhang et al. 2009). A large amount of drug could be delivered to cancer cells for targeting biorecognition events (Ferrari et al. 2005), and make it possible to reach steady state cytotoxic drug concentration at the tumor site over an extended period of time. In addition, the combination of targeted delivery and controlled release could decrease the likelihood of significant systemic toxicity since the drug is encapsulated and biologically unavailable during transit in systemic circulation. Use of poly (D, L-lactide) and poly(glycolide) and their copolymer poly (D,L-lactide-co-glycolide) (PLGA) are the most commonly used biocompatible polymers that have been extensively reviewed in the past (Avgoustakis et al. 2004, Astete and Sablòv 2006; Shive et al. 1997) and are currently being extensively investigated for controlled release of drugs (Holgado et al. 2011, Misra et al. 2011).

Monoclonal Antibodies

FDA in 1986 approved the first monoclonal antibody muromonab-CD3 (Orthoclone OKT3), which prevents acute organ rejection after transplantation by blocking T-cell function. Since then several other monoclonal antibodies have been approved about one half of them for the treatment of cancer (Table.1). The fragment antigen binding (Fab) of a monoclonal antibody, which recognizes and binds to antigens is responsible for the highly specific targeting that is possible with such therapies. Monoclonal antibodies exert their anticancer effects through a variety of mechanisms; by recruiting host immune functions (including natural killer cells and the complement cascade) to attack the target cell; by binding to ligands or receptors thereby interrupting essential cancer cell processes or by carrying a lethal payload such as a radioisotope or toxin to the target cell (i.e. conjugated monoclonal antibodies) (Adams et al. 2005, Xu et al. 2008). Because their protein structure is denatured in the gastrointestinal tract, monoclonal antibodies are administered intravenously. They do not undergo hepatic metabolism and are not subjected to significant drug interactions.

Nanoparticle-aptamer bioconjugates

This novel approach of using aptamers as targeted ligands on drug-encapsulated nanoparticles, proved to be highly effective in targeting cancer cells and decreasing encapsulated tumor size (Farokhzad and Teply 2006). Aptamers are DNA or RNA oligonucleotides that fold in tertiary conformations which are then able to bind to targeting antigens (Ellington and Szostak 1990). They are advantageous because aptamers are fairly small in size and therefore do not significantly impact the particle’s overall size. Aptamers are also non-immunogenic and fairly stable with long circulation time in the body. Aptamers have high affinity and specificity which is an important requirement in targeting (Farokhzad and Langer 2006; Lassalle et al. 2011, Cerchia et al. 2011, Agnes et al. 2012). The use of docetaxel-encapsulated nanoparticle-aptamer bioconjugates demonstrated a decrease in tumor size from approximately 300 mm² to 120 mm². In addition to reducing tumor size, these targeting methods had fewer side effects on healthy cells within the body in comparison to current methods.
of chemotherapy (Farokhzad and Teply, 2006). Table 2 provides list of aptamers, their specific target and application for cancer targeting.

**Oligopeptide-based targeting molecules**

Peptides have gained a lot of attention as a potent targeting ligand. The recent success is the development of peptide phage libraries (~1011 different peptide sequences), a bacterial peptide display library, a plasmid peptide library and new screening technologies. Combinatorial libraries have led to the discovery of short peptides (10-15 amino acids) that are able to bind to targeted proteins, cells or tissues specifically (Shukla et al. 2005, 2005a, Brissette et al. 2006, Krag et al. 2006; Newton et al. 2006, Bhutia and Maiti, 2008, Zhou et al. 2010). Peptides are becoming an attractive alternative to antibodies because of their small size, lower immunogenicity, higher stability and ease of manufacture. For Example, a cyclic arginine-glycine-aspartic acid (RGD) peptide that binds to integrins (Burke et al. 2002) is currently in phase II clinical trials for the treatment of non-small cell lung cancer and pancreatic cancer. Despite the success listed above, RGD-targeted therapy still encounters many challenges. First and foremost is the limitation associated with the nonspecific adhesive nature of the RGD-integrin targeting system. Integrins are extracellular receptors that are not only expressed on cancer cells but also on virtually all epithelial cells and are therefore not cancer specific (Bibby et al. 2005, Montet et al. 2006). Recent development of phage display screening methods has successfully isolated peptide ligands with high specificity and affinity to cell-surface reproductive hormone receptors (Zhang and Xu, 2011; somatostatin receptors (Saveanu et al. 2006, Carrasquillo and Chen, 2010), tumor vasculature antigens (Cortijo et al. 2006, Staquicini et al. 2011). Peptides bind specifically to tumor vasculature in patients and show potential as a platform for an in vivo phage library selection (Arap et al. 2002). The development of protocols to select potent peptides as targeting ligands will lead to the clinical translation of new technologies for cancer therapy and diagnosis (Zhang et al. 2012)

**Folate-based targeting molecules**

One of the most extensively studied small molecule moiety for drug delivery is folic acid (folate). This high-affinity vitamin is a commonly used ligand for cancer targeting because folate receptors (FRs) are frequently over-expressed in a range of tumor cells (Antony et al. 1992). Folate specifically binds to FRs with a high affinity (KD = ~10-9 M), enabling a variety of folate derivatives and conjugates to deliver molecular complexes to cancer cells without causing harm to normal cells. It has been used as a targeting moiety combined with a wide array of drug delivery vehicles including liposomes (Hong et al. 2011), protein toxins, polymeric NP (Zhang et al. 2010), linear polymers, and dendrimers (Zili et al. 2010) to deliver drugs selectively into cancer cells using FR-mediated endocytosis (Quintana et al. 2002, Benns et al. 2002).

**AdNectins**

AdNectins represent another class of novel targeting molecules derived from the tenth type III domain of human fibronectin (Ramamurthy et al. 2012). AdNectins are thermostable and protease-resistant oligopeptides that were initially derived from the 10FN3 domain of human fibronectin (Xu et al. 2002, 2003). Each AdNectin typically has three distinct loop structures. A large library of AdNectins has been created by introducing diversity into these loops. Recently, an AdNectin for human vascular endothelial growth factor receptor 2 (VEGFR2) named angicept (Getmanova et al. 2006) has been isolated and entered Phase I clinical trials for treating advanced solid tumors and non-Hodgkin’s lymphoma. These antibody fragments and oligopeptides have shown promising targeting results. Conjugation of these molecules on drug-encapsulated NP may further enhance targeted chemotherapy.

**Microfluidics**

Microfluidics is the science and technology of manipulating nanoliter volumes in microscale fluidic channels (Whitesides et al. 2006). Manz and Verpoorte have shown that several labor-intensive and time-consuming steps such as sample preparation, purification, mixing, reactions, separation and detection could be performed on a single monolithic micro-fabricated device (Manz et al. 1990, Verpoorte et al. 1992). Miniaturization in conjunction with integration of
### Table 1: Monoclonal Antibodies for Cancer Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antibody type</th>
<th>Indications</th>
<th>Toxicities, side effects, and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Humanized, Un conjugated</td>
<td>Chronic Lymphocytic leukemia</td>
<td>Hematologic toxicity; opportunistic infections; rash.</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Humanized, Un conjugated</td>
<td>Colorectal cancer, non-small cell lung cancer</td>
<td>Gastrointestinal perforation; wound healing complications; hemorrhage; arterial and venous thrombo embolism; proteinuria; hypertension.</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Chimeric, unconjugated</td>
<td>Colorectal cancer, head and neck cancers</td>
<td>Acneiform rash; diarrhea; hypomagnesemia; nausea and vomiting; interstitial lung disease (rare)</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Humanized, Toxin conjugate (calicheamicin)</td>
<td>Acute myeloid leukemia</td>
<td>Severe myelosuppression; hepatotoxicity</td>
</tr>
<tr>
<td>90Y-Ibritumomab tiuxetan</td>
<td>Murine, radioisotope conjugate (yttrium-90)</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Severe, prolonged myelosuppression; severe mucocutaneous reactions (risk of secondary malignancies (e.g., acute myeloid leukemia)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Human, Un conjugated</td>
<td>Colorectal cancer</td>
<td>Acne form rash; diarrhea; hypomagnesaemia; hypocalcaemia; nausea and vomiting</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric, Un conjugated</td>
<td>Non-Hodgkin’s lymphoma, rheumatoid arthritis</td>
<td>Lymphocytopenia; HBV reactivation; severe mucocutaneous reactions</td>
</tr>
<tr>
<td>131I-Tositumomab</td>
<td>Murine, radioisotope conjugate (iodine-131)</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Hypothyroidism; severe, Prolonged myelo-suppression; nausea and vomiting; secondary malignancies (e.g., acute myeloid leukemia)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Humanized, Un conjugated</td>
<td>Breast cancer with HER2/neu over expression</td>
<td>Cardiomyopathy (especially if co administered with anthracycline chemotherapy); cytopenias; rash</td>
</tr>
</tbody>
</table>

### Table 2: Aptamers for targeting cancer

<table>
<thead>
<tr>
<th>Aptamer</th>
<th>Specific target</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>A30</td>
<td>Human epidermal growth factor receptor-3</td>
<td>Binds to the cancer cell surface</td>
</tr>
<tr>
<td>A9,A10</td>
<td>Prostate-specific membrane antigen</td>
<td>Binds to the cancer cell surface</td>
</tr>
<tr>
<td>AS-1411</td>
<td>Nucleolin</td>
<td>Binds to the cancer cell surface</td>
</tr>
<tr>
<td>Clone 5</td>
<td>Sialyl Lewis X</td>
<td>Binds to the cancer cell surface</td>
</tr>
<tr>
<td>CTLA-4 aptamer</td>
<td>Cytotoxic T cell antigen-4</td>
<td>Binds to T cells</td>
</tr>
<tr>
<td>TTA1</td>
<td>Fibrinogen-like domain of tenascin-C</td>
<td>Binds to extracellular matrix proteins</td>
</tr>
<tr>
<td>PDGF-r aptamer</td>
<td>Platelet derived growth factor receptor</td>
<td>Binds to microvasculature</td>
</tr>
<tr>
<td>III.1</td>
<td>Pigpen</td>
<td>Binds to microvasculature</td>
</tr>
</tbody>
</table>
multiple functionalities, which harness unique microscale phenomena, has led to microfluidic systems that perform better than macroscale systems, reduce labor input and have the potential for low-cost mass production (Whitesides et al. 2006, Saurabh et al. 2010). Since then the field of microfluidics has blossomed and is now poised to impact areas as diverse as chemical synthesis, biological analysis, optics, information technology, forensics and environmental monitoring.

The ability of microfluidic systems to mix reagents rapidly and provide homogeneous reaction environments continuously vary reaction conditions, enable rapid temperature control and allow addition of reagents at precise time intervals during the progress of a reaction, are some of the key features that have made microfluidic systems useful for the synthesis of NP (DeMello et al. 2004). For example, millisecond timescale control of reaction conditions in a droplet-based microfluidic device has enabled the synthesis of highly monodisperse CdS NPs and CdS/CdSe core-shell NP (Shestopalov et al. 2004). Microreactors enable screening through a variety of reaction conditions by systematically varying flow rates, temperature and concentrations. The optimal reaction conditions for CdSe NP synthesis have been identified in this way using very small amounts of reagents (Yen et al. 2003). Microfluidic devices have since then been used for the synthesis of high-quality CdS, CdSe, Ag, Pd, Cu, and CdSe/ZnS core-shell NP (deMello et al. 2006).

Nanotechnology for cancer targeting

The current age is characterized by accelerating technological development and NT (Nanotechnology) is developing extraordinarily rapidly. The field was not identified until 1959, when Nobel physicist Richard Feynman called attention to the opportunities in the realm of the "staggeringly small". In 2001, Science magazine named nanotechnology the "breakthrough of the year." Currently, there are several hundred different commercial applications of NT (Roco and Bainbridge, 2000). The National Science Foundation predicts that nano-related goods and services could be a $1 trillion market by 2015.

Nanotechnology has the potential to offer solutions to these current obstacles in cancer therapies, because of its unique size (1-100nm) and large surface-to-volume ratios (McNeil et al. 2005). Nanotechnologies may have properties of self-assembly, stability, specificity, drug encapsulation and biocompatibility as a result of their material composition (Grodzinski et al. 2006). The NCI Alliance for Nanotechnology in Cancer has identified the potential of nanotechnology and aims to accelerate the application of nanotechnologies in cancer research and clinical development. This program is a comprehensive, systemized initiative encompassing both public and private sectors (Ferrari et al. 2005). The program comprises of eight Centers of Cancer Nanotechnology Excellence (CCNE), twelve platform projects and four interdisciplinary training programs across the nation (Ehdaie et al. 2007). Thus far research programs within the Alliance have made remarkable advancements in nanotechnology-cancer research.

The integration of nanotechnology with biotechnology and medicine means the ability to uncover the structure and function of biosystems, which intrinsically have an organizational level at the nanoscale. In other words, nanotechnology provides the tools to measure and understand biosystems (Roco et al. 2003). More specifically nanotechnology is being translated into nanomedicine thereby referring to treatment and curing of diseases at a molecular scale. Use of nanoparticles (100 nm or smaller) for delivery and targeting of therapeutic and diagnostic agents is at the forefront of projects in cancer medicine. The targeting and accumulation of drugs to specific sites where the agent is released provides a means to reach high drug concentration at a designated area with far less systemic side effects. Likewise, medical imaging may make a gigantic step forward with the use of nanoparticles with super paramagnetic properties for magnetic resonance imaging (MRI). These developments harbor favorable prospects for diagnostic and therapeutic applications in oncology. Generally in the size range of 1–100 nm, these drugs have emerged as novel antitumor agents because they have the potential to deliver high concentrations of drugs to cancer cells and cause less toxicity than systemically administered drugs. The nanoparticles are the same size as a virus, but look like water droplets to the immune system and the immune system ignores them.
The first nano drug sanctioned by the FDA for breast cancer was Abraxis BioScience’s Abraxane in 2005 for the treatment of metastatic disease. It was made possible by a nanoparticle albumin-bound (nab) technology. The other approved nanodrug is pegylated liposomal doxorubicin, which is marketed as Doxil in the U.S. by Centocor Ortho Biotech and in Israel by Janssen-Cilag for ovarian cancer that has progressed or recurred after platinum-based chemotherapy. A significant justification for approving Doxil/Caelyx had been the reduction of associated significant toxicities including cardiomyopathy, bone marrow depression, alopecia and nausea rather than the enhancement of clinical efficacy.

Drug developers are thus attempting to enhance the value of anticancer nanodrugs beyond reduced toxicity. The aim is to create second-generation nanotherapeutics that has greater specificity, target selectivity and an improved therapeutic index. For example, preclinical studies have shown that doxorubicin-loaded liposomes conjugated with folic acid can be internalized upon binding with folate receptors on cancer cells. This suggests the potential for improved targeting and a subsequent internalization strategy in the treatment of several multidrug-resistant tumors. And doxorubicin-loaded long-circulating liposomes modified with RGD-peptide motif can reportedly target the neovascularation of angiogenic tumors.

In 2006 Sathe demonstrated the use of nanotechnology in cancer detection (Sathe et al. 2006). Nanoparticle technologies are under development and testing as candidate multifunctional, molecularly or physically targeted contrast agents for all clinical imaging modalities, with the objectives of detecting smaller and earlier-stage cancer tumors, identifying molecular expressions of neoplasm and their microenvironment and providing improved anatomical definition for lesions (Sullivan et al. 2004). Nanotechnology is now overcoming challenges of early detection and imaging in current cancer therapies (Banerjee and Sengupta, 2011, Palakurthi et al. 2012, Ranganathan et al. 2012).

Conclusion

Targeted therapy seems a promising approach against cancer in order to enhance the efficacy and to reduce the side effects of antitumor agents through high selectivity. One of targeted strategies is to use tumor-specific ligands as targeting moieties to carry drugs into tumor cells, and use the receptors that expressed on tumor cells as target sites. In this context active targeting of cancer cells through interactions mediated by ligands such as antibodies, lectins, aptamers, folate, and peptides as presented with nanoparticles offer a promising strategy for cancer therapy. Over the past few decades, interest in designing and developing polymeric nanoparticles (NP) has undergone considerable explosion. Indeed, these nanoparticulated polymer-based systems provide potential solution to improve therapeutic efficacy and diagnosis sensitivity. NPs can provide the means to deliver drugs at a prolonged rate to specific cancer targets. Once optimized, these targeted NPs will provide the improved treatment options that are so urgently sought for cancer. Recent progress in cancer nanotechnology raises exciting opportunities for personalized oncology in which diagnosis and treatment are based on the molecular profiles of individual patients, and make cancer treatment specific, efficient and targeted to specific tissue with less toxicity.

Acknowledgement

Extramural Senior Research Fellowship grant (31/21(86)/2010-EMR-1) from Council of Scientific and Industrial Research, New Delhi-110012, is highly acknowledged.

REFERENCES


http://dx.doi.org/10.1073/pnas.0407218101
PMid:15520369 PMCID:528737


PMid:16682734


69 | International Journal of Life Sciences • ISSN 2091–0525 • Year 2012 • Volume 6 • Issue 1
Review article


Najar et al. (2012)


Review article

*Najar et al. (2012)*


Submit your next manuscript to IJLS with a -

© International Journal of Life Sciences (IJLS)