

Cancer Nanotechnology: The Recent Developments in the Cancer Therapy

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Abstract

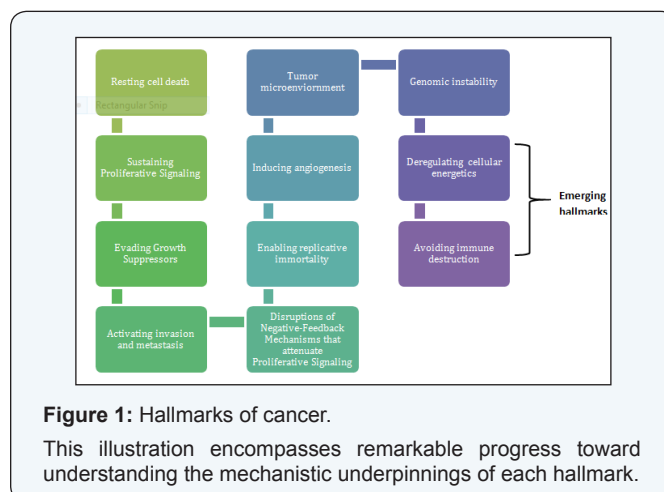
The nanotechnology is prominent in medicine for various applications. Nanotechnology is a multidisciplinary field, which covers diverse arrays of devices made using principles of engineering, biology, physics, and chemistry. The increasing number of nanomedicines is approved clinically, used safely, which highlights the important role of nanotechnology in the field of cancer research. The successful application of nanotechnology to the targeted smart drug therapy ISA rapidly growing component of armamentarium against cancer. Nanotechnology is being applied to cancer in two broad areas: the development of nanovectors, such as nanoparticles, which can be loaded with drugs or imaging agents and then targeted to tumors, and high throughput nanosensor devices for detecting the biological signatures of cancer. This advanced technology provides a unique approach and comprehensive technology against cancer through early diagnosis, prediction, prevention, personalized therapy, and medicine. This review focuses on nanotechnology-based clinical approaches in the advancements of cancer therapy.

Keywords: Nanotechnology; Nanosystems; Targeted therapy; Cancer therapy; Nano-oncology

Abbreviations: NPs: Nanoparticles; NM: Nanomedicine; FDA: Food and Drug Administration; HER2: Human Epidermal Growth Factor Receptor 2; ADC: Antibodies-Drug Conjugates; RNAi: RNA Interference; PSMA: Prostate-Specific Membrane Antigen; EPR: Enhanced Permeability and Retention; mAbs: Monoclonal Antibodies

Introduction

Cancer is a leading cause of death worldwide. American cancer society estimates that in 2016, there will be an estimated 1,685,210 new cancer cases diagnosed and 595,690 cancer deaths in the US [1]. About 595,690 Americans are expected to die of cancer in 2016, which translates to about 1,630 people per day. Cancer is the second most common cause of death in the US, exceeded only by heart disease, and accounts for nearly 1 of every 4 deaths. Cancer is a complex disease to understand because it comprises six biological capabilities acquired during the multistep development of human tumors [2,3] they include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks is genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. However in the last decade, two emerging hallmarks are reprogramming of energy metabolism and evading immune destruction (Figure 1).



Most human cancers are treated by surgical resection, chemotherapy, and/or radiation. Surgery cures ~45% of all patients with cancer, whereas chemotherapy and radiation therapy together cure only 5%, and the remainder succumbs to their diseases [4]. Limitations in cancer treatment is a result

of current challenges seen in cancer therapies, including lack of early disease detection, nonspecific systemic distribution, inadequate drug concentrations reaching the tumor, and inability to monitor therapeutic responses. Poor drug delivery and residence at the target site leads to significant complications, such as multi-drug resistance [5].

Several challenges noticed and well reported by current cancer therapies include nonspecific systemic distribution of antitumor agents, inadequate drug concentrations reaching the tumor site, intolerable cytotoxicity, limited ability to monitor therapeutic responses and development of multiple drug resistance. The most troublesome issues of current cancer treatment are drug toxicity and tumor resistance. Toxicity can cause major complications, such as low white-blood-cell counts or heart failure that necessitates cessation of treatment [6-8]. Evolution of drug resistance by tumors accounts for the vast majority of cases in which treatment fails. At present, the early recognition and treatment of cancer remain a technological bottleneck. Despite many advances in conventional treatment

options such as chemotherapy and radiation, cancer therapy is still far from optimal because it is plagued by some drawbacks. Thus, there is an urgent need and major opportunities to develop new and innovative technologies [9]. To overcome the above challenges associated with cancer treatment safety and efficacy, many scientists have taken tremendous efforts to introduce smart targeted therapy, using advanced nanotechnology to fight against the lethal killer cancer. Nanotechnology-based therapeutics have exhibited clear benefits when compared with unmodified drugs, including improved half-lives, retention, targeting efficiency, and fewer patient side effects (Figure 2 & Table 1).

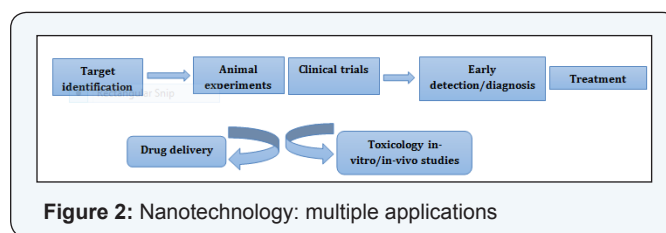


Figure 2: Nanotechnology: multiple applications

Table 1: Applications of nanotechnology.

Applications	Without use of Nanotechnology	With use of Nanotechnology
Diagnosis	FNAC, biopsy, FISH, immune histo chemistry used for diagnosis. Early detection is not possible Only in vitro detection is possible Real time detection is not possible	Quantum dots and raman probe can be used for diagnosis Early detection is possible In vitro and in vivo detection is possible Real time detection is also possible
Imaging	X-ray, CT scan, MRI,PET scan, isotopes can be used Ultrasonography is used	Quantum dots can be used UCM ultrasonography can be used Very early detection of neo vascularization is possible Imaging, targeting, delivering and monitoring is possible
Early detection of cancer	Cytology, FNAC and biopsy is used	Vital optical imaging is possible Inexpensive mass screening is possible
Drug delivery	Oral, intramuscular ,intra vinous, intra-arterial drug delivery is possible	Targeted delivery is possible Possible to deliver small dose Low systemic toxicity Batter and faster responses

Early detection, imaging, diagnosis and drug delivery with and without use of nanotechnology.

Nanomedicines platform, drug targeting strategies


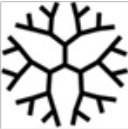
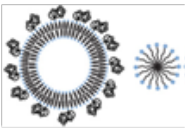




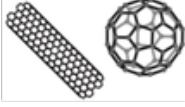
Nanomedicine is a rapidly growing area of medical research that is focused on developing nanoparticles (NPs) for prophylactic, diagnostic, and therapeutic applications. Recently nanocarriers (particularly in the size range of 10 nm to 100 nm) have been an emerging class of therapeutics for cancer treatment. In addition liposomal doxorubicin, albumin-bound and paclitaxel (Abraxane1) is FDA approved Nanosystems used

in clinical practice [10]. Nanoparticles platforms can be broadly categorized as organic, inorganic and hybrid (Table 2). Organic nanoparticles have been widely explored for decades, yielding a large variety of materials, formulations, imaging modalities, and targets for cancer therapy [11]. Nanotechnology is gaining importance in biology due to its small size and targeted effects. Nano-devices are 100-10, 000 times smaller than the human cell. Due to the smaller size and larger surface area relative to

their volume, Nanosystems can easily interact with the surface of the cell and inside of the cell. By interacting with cellular proteins Nanosystems can have the potential to detect tumor microenvironment and deliver drug treatment [12]. Nanosystems have four unique properties that distinguish them from other cancer therapeutics: (i) the Nanosystems can themselves have therapeutic or diagnostic properties and can be designed to carry a large therapeutic 'payload'; (ii) Nanosystems can be attached to multi valet targeting legends, which yield high affinity and

specificity for target cells; (iii) Nanosystems can be made to accommodate multiple drug molecules that simultaneously enable combinatorial cancer therapy and (iv) Nanosystems can bypass traditional drug resistance mechanisms. By using both passive and active targeting strategies, the nanocarriers can achieve increased intracellular concentration of drugs in cancer cells while minimizing toxicity in normal cells, simultaneously enhancing anti cancer effects and reducing systemic toxicity.

Table 2: Summary of nanoparticles platforms for nanomedicine used for cancer therapy (11).

	Particle type	Properties	Applications
	Polymer	Some biodegradable	Drug delivery; passive release (diffusion), controlled release (triggered)
	Dendrimer	Low poly dispersity, cargo, biocompatible	Drug delivery
	Lipid	Can carry hydrophobic cargo, biocompatible, typically 50–500nm	Drug delivery
	Quantum dots	Broad excitation no photo bleaching, Tunable emission, typically 5–100nm	Optical imaging
	Gold	Biocompatibility, typically 5–100nm	Hyperthermia therapy, drug delivery
	Silica	Biocompatibility	Contrast agents, drug delivery (encapsulation)
	Magnetic	Super paramagnetic, ferromagnetic (small reminisce to minimize aggregation), super ferromagnetic (~10nm), paramagnetic	Contrast agents(MRI), hyperthermia therapy
	Carbon-based	Biocompatible	Drug delivery

Drug targeting strategies

To achieve the effective drug delivery two basic fundamental principles should be involved first the drug should able to reach the desired tumor site after administration with the minimal

loss of their volume and activity in blood circulation. Secondly, drugs should only kill tumor cells without harmful effects to healthy tissue. These requirements may be enabled using two strategies: passive and active targeting of drugs [12] (Figure 3).

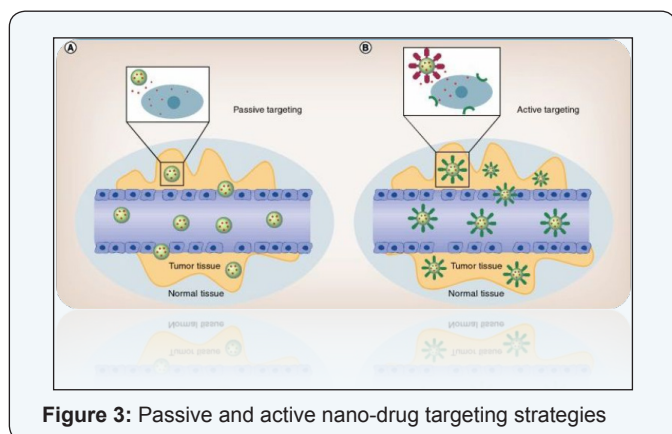


Figure 3: Passive and active nano-drug targeting strategies

Passive targeting systems include liposomes, micelles, gold particles, iron oxide nanoparticles, silica nanoparticles, quantum dots, and hybrid nanoparticles. Passive targeting takes advantage of the unique path physiological characteristics of tumor vessels, enabling nondrug to accumulate in tumor tissues. Typically, tumor vessels are highly disorganized and dilated with a high number of pores, resulting in enlarged gap junctions between endothelial cells and compromised lymphatic drainage. The 'leaky' vascularization, which refers to the EPR effect, allows migration of macromolecules up to 400 nm in diameter into the surrounding tumor region. Drug carriers are expected to stay in the blood for a long time, accumulate in pathological sites with affected and leaky vasculature (tumors, inflammations, and infarcted areas) via the enhanced permeability and retention (EPR) effect, and facilitate targeted delivery of specific legend-modified drugs and drug carriers into poorly accessible areas [13]. Although passive targeting approaches form the basis of clinical therapy, they suffer from several limitations like some tumors do not follow EPR phenomena and some tumors are highly unorganized tumor mass. One way to overcome the limitations of passive targeting is to attach high-affinity legends such as aptamers, antibodies, small molecule, or peptides that will only bind to specific cellular receptors. Active targeting is an alternative strategy to overcome the limitations of the passive method. Active method conjugates with target ligand or an antibody to nanoparticles. This ligand-target approach is expected to deliver drug efficiently at the active site [14].

Choice of target receptor

A design of targeted nanoparticles crucially depends on, selection of appropriate receptors or antigens locally expressed on cancer cells. Importantly ideal receptors or antigens are those which are uniquely expressed only on cancer cells and not on normal cells. In addition, these targets should also have a high density on the surface of the target tumor cells. Targeted Nanoconjugate should internalize after binding with ligands to avoid simple diffusion of the drug near the cell surface. However, this drug transport mechanism outside the cell may disperse or redistribute the drug to the surrounding normal tissues, instead of cancer cell mass. Internalization of target receptor via

receptor-mediated endocytosis triggers the drug release pattern specifically into cancer cells [14].

Choice of targeting ligand

Selective and successful drug transport mechanisms to the cancerous tissue are the emerging challenges. The choice of ligands has a great role in triggering receptor-mediated endocytosis. Ligands targeting cell-surface receptors can be natural materials like foliate and growth factors, which have the advantages of lower molecular weight and lower immunogenicity than antibodies. Recent advances in molecular biology and genetic engineering allow modified antibodies to be used as targeting moieties in an active-targeting approach. MAbs or antibody fragments (such as antigen-binding fragments or single-chain variable fragments) are the most frequently used ligands for targeted therapies. Compared with whole mAbs, the use of antibody fragments as a targeting moiety can reduce immunogenicity and improve the pharmacokinetic profiles of nanoparticles. For example, liposome's coupled with mAb fragments instead of whole antibodies showed decreased clearance rates and increased circulation half-lives, allowing the liposome's sufficient time to be distributed and bind to the targeted cells. This strategy improved the therapeutic efficacy of immune liposomal DOX targeted against CD19 on human B lymphoma cells in animal models [15, 16].

Nanotechnology-based advanced technologies

In the treatment of cancer, targeted therapy is desirable due to specificity to cancer cells and normal cells are not affected. Nanotechnology-based approaches are very recent and non-invasive strategies. Bioengineered nanoparticles or nanosystems are new armamentaria in cancer therapy which includes photo dynamic therapy (PDT), radiotherapy and radiofrequency therapy, and theranostics (Figure 4).

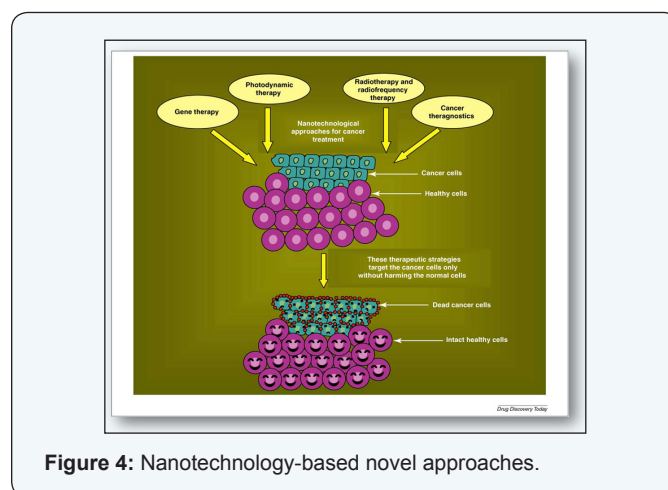


Figure 4: Nanotechnology-based novel approaches.

FDA approved Nanomedicines: An update in cancer therapy

Researchers have already made progress with chemotherapeutic Nanomedicine in the clinic. Nanomedicines have demonstrated the potential for increasing bio availability, enhancing drug solubility, active targeting, and high drug loading [17].

Several compounds that are in various stages of trials or already approved by the US Food and Drug Administration (FDA). For example, Calando Pharmaceuticals has demonstrated the first evidence of nanoparticles-delivered clinical RNA interference (RNAi). BIND Biosciences has shown that nanoparticles combining a chemotherapeutic drug with prostate-specific membrane antigen (PSMA) can reduce lung and tensile lesions with greater efficacy compared with the drug alone, and at substantially lower doses. Furthermore, Celgene's Abraxane. Doxil, daunoxome, Oncaspar, Depocyt and those in Nano-platforms that have reached an advanced stage of clinical development utilizing liposome's, lipid nanoparticles, lipoplexes, albumin nanospheres, thermo sensitive devices, micelles and gold nanoparticles [18]. An albumin-functionalized paclitaxel formulation was initially approved by the FDA for sale

as a breast cancer therapy, but also recently received approval for the treatment of lung and pancreatic cancers [9]. (Table 3) Additionally, the FDA approved antibodies-drug conjugates (ADC) such as brentuximab, abvedotin, trastuzumab emtansine and Marqibo, Brentuximab, abvedotin and Trastuzumab, emtansine conceptually one of the simplest Nanomedicine conjugated to a targeting molecule. Brentuximab targets the proteinCD30, a glycosylated phosphoprotein expressed by Bcells, including Bcell lymphomas, some leukemia's, and melanoma cancer stem cells. Trastuzumab targets the human epidermal growth factor receptor 2 (HER2) over expressed in HER2 positive breast cancer. However, there remain many challenges in exploiting advances in nanotechnology and bioengineering to develop systems that will have a significant impact on patient survival rates.

Table 3: Examples of FDA approved Nanomedicines for cancer and those undergoing clinical trials.

Drug product	Active ingredient	Manufacturer	Indications	FDA approved date / clinical trial status
Doxil (Caelyx) Pegylated	Pegylated doxorubicin	Ortho biotech, Schering-Plough	Ovarian/breast cancer	November 1995
Abraxane	Albumin-bound Paclitaxel nanospheres Nab paclitaxel in combination with gemcitabine	Abraxis Bioscience Astrazeneca Celgene's	Various cancers Metastatic pancreatic cancer	Jan-05 September 2013
Myocyte	Liposome capsulated Doxorubicin	Elan Pharmaceuticals/ Sopherion Therapeutics	Breast cancer	2000, Approved in Europe and Canada
Daunoxome	Liposome capsulated Daunorubicin	Gilead Science	HIV-related Kaposi sarcoma	Apr-96
Depocyt	Liposomal Cytarabine	Skye Pharma, Enzon	Lymphomatous Meningitis	Apr-99
Oncaspar	PEGasparaginase	Enzon	Acute Lymphocytic Leukemia	Feb-94
Onco-TCS	Liposomal Vincristine	Inex	Non-Hodgkin Lymphoma	In clinical phase I/II
LEP-ETU	Liposomal Paclitaxel	Neopharma	Ovarian/breast/lung cancers	In clinical phase I/II
Aroplatin	Liposomal Cisplatin analog	Antigenic, Inc	Colorectal cancer	In clinical phase I/II
ThermoDox	Doxorubicin	Cessions Corporation	Hepato cellular carcinoma	In clinical phase III

Discussion and Conclusion

Nanomedicine refers to the application of nanotechnology in medicine, and endeavors to diagnose, treat, and/or monitor disease on a nanoscale. Cancer nanotechnology is a quickly evolving field of inter disciplinary research that involves the biomedical application of nanoparticles, which are nanoscale devices that are able to overcome biological barriers, specifically, recognize a single type of cancer cell, and accumulate preferentially in tumors. Medical applications with nanoparticles are growing, as they have the potential to offer novel methods of noninvasive cancer detection, diagnosis, and treatment. Tumor targeting ligands, such as antibodies, peptides, or small molecules, can be attached to nanoparticles for targeting of tumor antigens and vasculatures with high affinity and specificity. In addition, diagnostic agents (i.e. optical, radiolabels, or magnetic) and chemotherapeutic drugs can be integrated into their design for more efficient imaging and treatment of the tumor with fewer side effects. Recent advances in nanomedicine raise exciting possibilities for future nanoparticles applications in personalized cancer therapy. nanotechnology has become an enabling technology for personalized oncology, in which cancer detection, diagnosis, and therapy are tailored to each individual's tumor molecular profile, and for predictive oncology, in which genetic and/or molecular markers are used to predict disease development, progression and clinical outcomes.

Nanomedicine holds much promise but there are still major areas of both basic and applied research in the area nanotechnology that needs to be explored to solve some of the existing problems. Nanooncology is the promising technology of the new era but significant obstacles have restricted the clinical translation of the cancer therapy. One of the main reasons for the restricted use of Nanomedicine is the matter of multifunctionality, multidrug resistance, and variable responses to standard therapy, complexities associated with heterogeneous mass of tumor cells, cancer stem cells, complicated therapy, and cross talk between several cellular pathways.

Overall considering potential applications of the Nanomedicine in the health sector, especially with regards to cancer therapy, there is an emerging need for the development of safety guidelines by the government. The emergence of Nanotechnology Research Centers, established in recent years (some of which are funded by the National Institutes of Health and the National Science Foundation), demonstrate the enthusiasm of investigators and granting agencies for the technology. In the next few years, many applications of nanotechnology will become commonplace within medical practice.

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