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TARGETED NANOTECHNOLOGY FOR ANTICANCER DRUG DELIVERY: CURRENT ISSUE AND CHALLENGE

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ABSTRACT

The main aim of nonmaterials is optimization on site of action at tumors cells as well least toxicity by its formulation. Only to progress the biodistribution of neoplasia drugs, nanoparticles are designed for optimal size and surface individuality to expand their flow time within the blood circulation. They are also proficient to carry their laden active drugs to cancer cells by using the single functional changes of tumors, as like their improved permeability and preservation result and the tumor microenvironment. In this study report, we have discussed the current status of nanoparticles developed as targeting delivery systems for anticancer drugs.

Keywords: Cancer, Drug Delivery, Nanomedicine, Chemotherapy, Liposome

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INTRODUCTION

Nanotechnology is the study, design, creation, synthesis, manipulation, and application of materials, devices, and systems at the nanometer scale. The prefix nano is derived from the Greek word dwarf. One nanometer is equal to one billionth of a meter, that is, 10^{-9} m[1]. The importance of particles in this range is in the sense that they can have different and enhanced properties compared with the same material at a larger size. Increased surface area and quantum effects are two principal factors separating nonmaterial's from other materials. These two factors can enhance properties such as reactivity, strength, electrical characteristics and *in vivo* behavior[2]. Nanotechnology and nanoscience are widely seen as having a great potential to bring benefits to many areas of research and applications[3]. The application of nanotechnology in the field of health care has come under great attention in recent times. There are many treatments today that take a lot of time and are also very expensive using nanotechnology, quicker and much cheaper treatments can be developed. Besides, there is another aspect to using nanotechnology in medicine. By using nanotechnology, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects[4]. Cancer is one of the leading diseases and although there are many drugs available for treatment, using nanotech based approach increases the activity as well as reducing the side effects profile many fold[5]. In this study, we aim to discuss the nanotech based approach, especially the use of NPs and their various forms in anticancer drug delivery.

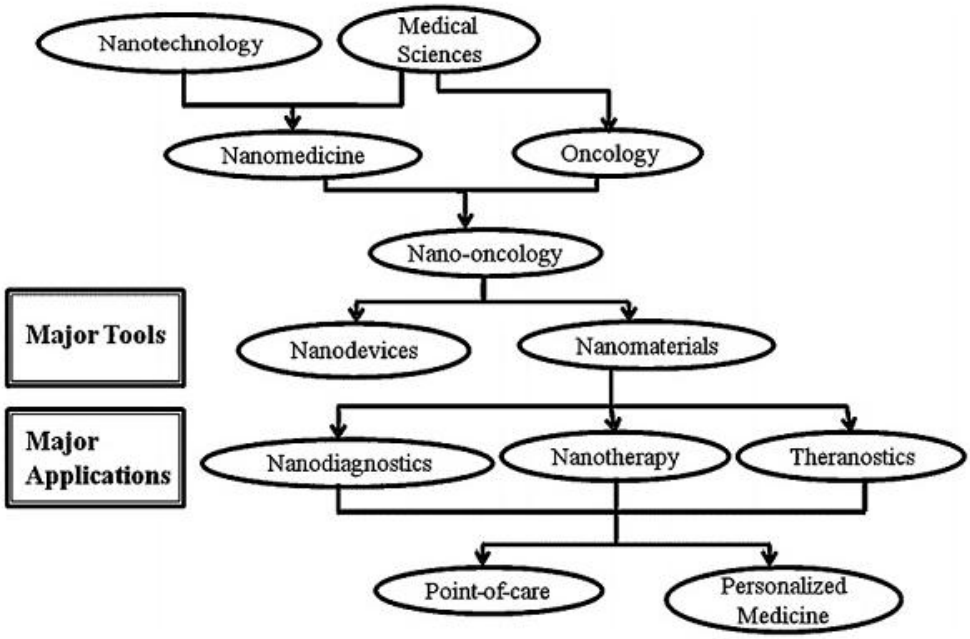

Figure 2: The relationship between nano-oncology and related fields[7]

LIMITATIONS OF CONVENTIONAL CHEMOTHERAPY

Chemotherapy act as effectual drugs treatment designed to inhibit cancer cells or to slow the indictment or proliferation of these cells. Despite this advantage, the effect of conventional chemotherapy produces also several disadvantages. The conventional chemotherapeutic agents don't destroy only the cancer cells, they damage also the healthy cells causing organ dysfunction, myelosuppression (occurs the reduced production of white blood cells), alopecia (hair loss), mucositis (inflammation of the mucous membranes lining the digestive tract) *etc.*[8, 9]. Other disadvantages of these chemotherapeutics are that they remain in the circulation for a very short time and cannot interact with the cancerous cells and also the poor solubility of the drugs represents a problem because making them unable to penetrate the biological membranes[10].

In several studies, it was reported that a problem for the administered drugs is represented by the surface of the cancerous cells because the surface is covered with a multidrug resistance protein (P-glycoprotein) acting like a reflux pump which prevents the drug accumulation in the tumor. Because of their numerous disadvantages, the researchers tried to replace the conventional chemotherapeutic agents with nanoparticles[11-12].

CANCER NANOTECHNOLOGY

Formal definitions of nanotechnological devices typically feature the requirements that the device itself or its essential components be man-made, and in the 1-1, 00 nm range in at least one dimension. Cancer-related examples of nano-technologies include injectable drug delivery nanovectors such as liposomes for the therapy of breast cancer[13-14]; biologically targeted nanosized magnetic resonance imaging (MRI) contrast agents for intraoperative imaging in the context of neuro-oncological interventions[15-16]; and novel, nanoparticle-based methods for high-specificity detection of DNA and protein[17].

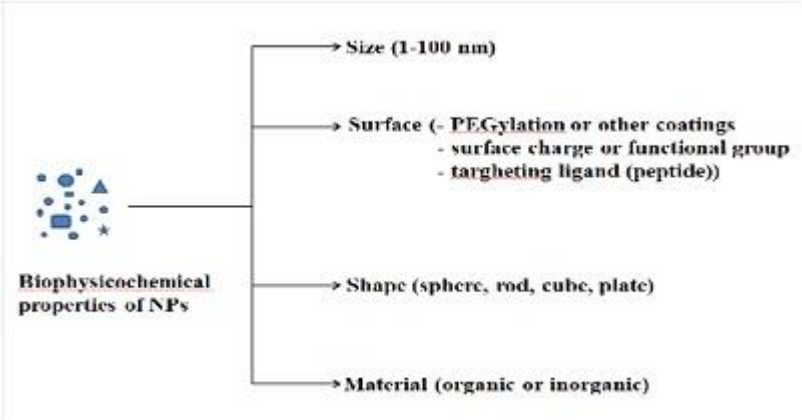

Figure 2 Biophysicochemical properties of NPs[18].

Table 1: Types of organic nanoparticles for cancer therapy[19]

Type of NPs	Size (nm)	Advantages	Disadvantages	Applications
Polymers	10-1000	Biodegradability, drug release	Low efficiency of delivery	Delivery of components
Quantum dots	<10	Surface modification	Unstable at UV	Detection of cancer
Dendrimers	43952	High drugs carriage	Cytotoxic	Target Delivery
Liposomes	50-100	Biodegradability	Inflammation	Gene delivery

DRUG DESIGN IN NANOMEDICINE: CANCER THERAPHY

Nanomedicine constructs are multicomponent systems, involving a carrier, therapeutic component, and often targeting moiety. Optimization of physicochemical properties of such constructs is challenging due to the interdependence of characteristics of individual components. Optimizing a construct (carrier þ drug molecule) as one unit and making this optimization part of an entire drug discovery process will allow nanotherapeutics to become a new class of drugs rather than being delivery vehicles for existing drugs[20]. This approach will bring greater flexibility to the design of APIs because drug properties (solubility, metabolism, bio-distribution, and target tissue accumulation) will reflect the combined properties of the drug molecule and nano-particle[21]. This will relax constraints on API chemical composition, as unfavorable physicochemical properties such as low plasma solubility, can be modified by association with the nano-particle. This streamlined nano-medicine development approach combined with preparation of high-throughput screening of large combinatorial libraries of nanoparticles with different properties is expected to produce a better path to nano-therapeutic optimization and should result in higher success rate of nanotherapeutics translation to clinical environment[22]. Recent works [5] demonstrated nanotherapeutic design optimization using screens of libraries containing up to 100 nanoparticle constructs with systematically varied physical and chemical properties, such as particle size, surface polyethylene glycol and ligand density, and drug release profile[23]. This library undergoes an iterative in vitro and in vivo screening process to optimize drug release, cell surface binding, pharmacokinetic/pharmacodynamic characteristics, biodistribution, and efficacy for a given indication. The broader use of such screening processes to include candidate APIs will lead to new classes of drugs along with well defined and possibly standardized processes of nanotherapeutic optimization[24]. Next-Generation Nanoparticles and Systems Materials science will continue to produce new and more functional nanosystems that are responsive to changes in pH, temperature, and enzymatic environment and can recognize changes in physiology or in the state of the disease. Similarly, external triggers such as light or applied electromagnetic fields can also be used to activate nanoparticles. Exploitation of external or physiologic triggers will allow for more sophisticated nanoparticle designs and programmed drug release. Rational and personalized design of nanoparticles, including optimization of pharmacokinetics and tumor accumulation in coordination with drug release kinetics and matching targeting ligand type and density to tumor antigen profile, was also discussed as a path to improving nanoparticle drug delivery performance[25]. The value of nanoparticles capable of penetrating biologic barriers was acknowledged in discussions about nanoparticle vehicle design. Greater focus should be placed on overcoming biologic barriers such as tumor stroma, the blood–brain barrier, and vascular endothelium, which inhibit effective delivery of drugs to tumor tissue. Nanoparticle designs effectively facilitating alternate routes of oral or nasal delivery in addition to predominantly used systemic delivery were also of interest to the workshop participants. One new and exciting area discussed at the workshop was biomimetic nanoparticle design[26]. This has already proved helpful in the development of new families of therapeutic nanoparticles: "leukolike" and "plateloids," which have properties that reproduce features of biologic cells to delay uptake by the mononuclear phagocyte system and penetrate across vascular endothelia (leukolike) or adhere firmly to the target vascular surface (plateloids). Another bioinspired approach is the development of cooperative systems of nanoparticles that exploit host signaling networks to generate superior functionalities. A system relying on the coagulation signaling cascade resulting from deliberately inflicted tissue damage to recruit "clot-targeted" nanomedicines to the tumor was recently demonstrated [6]. These systems demonstrate communication and bioresponsive capabilities that go well beyond the traditional design of contemporary nanoparticles for drug delivery[27].

TARGETED CANCER NANOTECHNOLOGY: THE CHALLENGES

In an ideal scenario, the onset of the transformational processes leading towards malignancy would be detected early, as a matter of routine screening, by non-invasive means such as proteomic pattern analysis from blood samples, or the *in vivo* imaging of molecular profiles and evolving lesion contours[28]. The biology of the host and the disease would be accurately determined, and dictate choices for targeting and barrier-avoiding strategies for intervention plan.Transforming cellular populations would be eradicated or contained, without collateral effects on healthy tissues, in a routine that could be repeated many times. Treatment efficacy would be monitored in real time. Therapeutics would be supplanted by personalized prevention. If fully integrated with the established cancer research enterprise, nanotechnology might help this vision become reality[29].

FUTURE PROSPECTS

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. In recognition of its potential impact in cancer research, the US National Cancer Institute has recently funded eight national Centers of Cancer Nanotechnology Excellence[30]. Looking into the future, there are several research themes or directions that are particularly promising but require concerted effort for success. The first is the design and development of nanoparticles with monofunctions or multiple functions. For cancer and other medical applications, important functions include imaging (single or dual modality), therapy (a single drug or a combination of two or more drugs) and targeting (one or more ligands). Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs and have shown they have a bright future as a new generation of cancer therapeutics. Furthermore, the development of multifunctional nanoparticles might eventually render nanoparticles able to detect and kill cancer cells simultaneously[31].

Although there are certain crucial questions and many challenges remaining for the clinical development of nanoparticles, as more clinical data are available, further understanding in nanotechnology will certainly lead to the more rational design of optimized nanoparticles with improved selectivity, efficacy and safety[32]. Current knowledge regarding the safety of nanocarriers, however, is insufficient. The pharmacokinetic behavior of different types of nanoparticles requires detailed investigation, and a database of health risks associated with different nanoparticles should be created. Preliminary and complementary animal studies should be carried out to identify the risks associated with nanoparticle use, with particular attention paid to elimination processes. Furthermore, very little attention has been paid to environmental effects and the potential effects on the health of those manufacturing these particles. Considering the countless potential applications of nanoparticles in the health sector, particularly in cancer research, there is an urgent need for the development of safety guidelines by the government[33]. The emergence of Nanotechnology Research Centers, established in recent years (some of which are funded through 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. Because these advancements will be incremental and will be initially derived from ongoing 'wet science' instead of scaled-down machining and computing, they might, ironically, sometimes be too small to be noticed[34].

CONCLUSION

The application of nanotechnology in the field of cancer nanotechnology has experienced exponential growth in the past few years. Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs and have shown they have a bright future as a new generation of cancer therapeutics. The multidisciplinary field of nanotechnology holds the promise of delivering a technological breakthrough and is moving very fast from concept to reality.

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