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RESEARCH ARTICLE

NANOTECHNOLOGY FOR CANCER APPLICATIONS: A REVIEW

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ABSTRACT

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The diagnosis and treatment of cancer represents a major area of unmet need across Europe and all other areas of the world. However, a strong connection between early detection and positive patient outcome: early detection is the best hope. The ability to assess health status, disease onset and progression, and monitor treatment outcome through a non-invasive method is the main aim to be achieved in health care promotion and delivery and research. There are three prerequisites to reach this goal: specific biomarkers that indicates a healthy or diseased state; a non-invasive approach to detect and monitor the biomarkers; and the technologies to discriminate the biomarkers. The early disease diagnosis is crucial for patient survival and successful prognosis of the emphasis of this chapter is on the recent advances on the biosensors for cancer detection and monitoring. An overview of biomarkers and biosensing systems currently used to detect the onset and monitor the progression of the selected diseases. The field of pharmaceutical and medical nanotechnology has grown rapidly in recent decades and offers much promise for Prevention, detection, and therapeutic advances. This review is intended to serve as a quick summary of the major areas in the cancer prevention, detection and therapeutic advances of nanotechnology.

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INTRODUCTION

As the causes of cancer are so diverse, clinical testing is also very complex. The multi-factorial changes (genetic and epigenetic) can cause the onset of the disease and the formation of cancer cells. However, no single gene is universally altered during this process, but a set of them that brings difficulties to the correct disease diagnosis. All the changes which take place, in the tumors from different locations (organ), as well within tumors from the same location, can be so variable and overlapping that it is difficult to select a specific change or marker for the diagnosis of specific cancers. Therefore, a range of biomarkers can potentially be analyzed for disease diagnosis. These biomarkers or molecular signatures can be produced either by the tumor itself or by the body in response to the presence of cancer [1]. In recent years, there is high demand in the field of medical diagnostics for simple and disposable devices that also demonstrate fast response times, are user-friendly, cost efficient, and are suitable for mass production. Biosensor technologies offer the potential to fulfill these criteria through an interdisciplinary combination of approaches from nanotechnology, chemistry and medical science. Cancer is defined as abnormal and uncontrolled cell growth due to an accumulation of specific genetic and epigenetic defects, both environmental and hereditary in origin. Unregulated cell growth leads to the formation of a tumor mass that over time becomes independent of normal homeostatic checks and balances. Tumor cells in essence become resistant to apoptosis and other antigrowth defenses within the body. As the cancer progresses, the tumor begins to spread beyond the site of origin and metastasize to other body organs and systems, at which point, the cancer is essentially incurable. The two major tumorigenesis mechanisms are activation of oncogenes and inactivation of tumor suppressor genes (TSGs). Activation of oncogenes occurs through mutation or duplication of a normal gene (a proto-oncogene) involved in the regulation of cell growth, proliferation, and/or differentiation. This typically results in constitutive activation or excess levels of a normal gene product, leading to the deregulation of cell growth, increased cell division, and tumor formation. Perhaps more so than any other type of oncogene, growth factor receptors have been investigated as potential cancer biomarkers. P53 protein is a master regulator of apoptosis or programmed cell death. Mutations in p53 are found in brain, breast, colon, lung, hepatocellular carcinomas, and leukemia. Another major concern with the loss of P53 is

that it can serve as a mechanism of chemotherapeutic drug resistance [2,3]. Utilization of nanotechnology for the development of efficient drug delivery systems is one of the most recent developments in medical science. The structure and tunable surfaces of nanoparticles allow them to encapsulate/conjugate single or multiple entities, adapting them as ideal transporters for various anticancer drugs [4].

Nanotechnology in Preventive Aspects

In general, the best way to eliminate a problem is to eliminate the cause. In cancer, the problem can be perceived differently at various stages of the disease. Most apparently, if genetic mutations are the underlying cause, then we must counteract the causes of the mutations. Unfortunately, genetic mutations are caused by artificial or natural carcinogens only some of the time. At other times, they may occur spontaneously during DNA replication and cell division. With present science and technology there is very little we can do to prevent this from happening. However, in all other cases, eliminating the carcinogens is indeed a highly effective way of cancer prevention. But most patients do not recognise the problem until it has actually occurred, which makes preventive medicine a rarely utilised, although a highly effective form of cancer prevention. Even so, is there a way to eliminate cancer through nanotechnology before it starts? Although there is little current research on preventive treatments using nanotechnology, they are indeed possible. After a careful review of the most advanced disease-time nanoscale treatment methods, one can easily see why the proposed nanotechnology alternatives to current preventive treatments have so strongly attracted the attention of the scientific and medical communities in recent years. To demonstrate the viability of the nanotechnology-based treatments, let us consider melanoma for example. Melanoma, a form of skin cancer, is caused primarily by ultraviolet radiation from the Sun. The current method of preventive treatment against bombardment with this kind of harmful radiation involves suspending a substance that either absorbs or scatters ultraviolet radiation in a thick emulsion. We use this emulsion, called sunscreen, to coat our skin prior to prolonged exposure to sunlight. Some of the problems with this method are that this emulsion can be easily rubbed off and can loose its effectiveness over time, thus needing to be reapplied periodically. Some very recent works have shown that it is possible to tag specific types of cells with nanoparticles by conjugating them to targeting agents designed to recognise cell-specific surface proteins [5]. Preventive treatments are not much good to those who have

already developed the disease. And since these are the people who require the most immediate medical help, it is no wonder that a majority of innovative treatments are focused here in Table No. 1. Again, there are several ways to view the problem. The traditional approach is to simply eliminate the causing agents, or the cells that make up the tumour and end their pararcine signalling effect. This method actually dates back to the mid-17th century, when John Hunter, a Scottish surgeon first suggested the surgical removal of the tumour [6].

Nanotechnology in detection of cancer cell

Electrochemical detection of rare circulating tumor cells has the potential to provide clinicians with a standalone system to detect and monitor changes in cell numbers throughout therapy, conveniently and frequently for efficient cancer treatment [7].Many commercially available platforms use fluorescence labels as the detection system. Biosensors can be designed to detect emerging cancer biomarkers and to determine drug effectiveness at various target sites. Biosensor technology has the potential to provide fast and accurate detection, reliable imaging of cancer cells, and monitoring of angiogenesis and cancer metastasis, and the ability to determine the effectiveness of anticancer chemotherapy agents.

Cancer biomarkers

The National Cancer Institute (NCI) defines a biomarker as "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition". Biomarkers can be of various molecular origins, including DNA (ie, specific mutation, translocation, amplification, and loss of heterozygosity), RNA, or protein (ie, hormone, antibody, oncogene, or tumor suppressor). Cancer biomarkers are potentially one of the most valuable tools for early cancer detection, accurate pretreatment staging, determining the response of cancer to chemotherapy treatment, and monitoring disease progression. Biomarkers are typically detected in human fluids such as blood, serum, urine, or cerebral spinal fluid, but they can also be present in or on tumor cells. A partial list of tumor biomarkers is presented in Table 2. [8]. These biomarkers or molecular signatures can be produced either by the tumor itself or by the body in response to the presence of cancer [1].Most of these biomarkers, however,

have yet to demonstrate sufficient sensitivity and specificity for translation into routine clinical use or for treatment monitoring. This is an area that biosensor technology can potentially improve upon. Markers that can be used for global screening purposes would enhance preventative cancer care at an early stage of ovarian cancer. For example, creatine kinase B(CKB) is highly expressed in early-stage (since stage I) of ovarian tumor tissues and is significantly elevated in the sera of ovarian cancer patients important development that will benefit patients is the construction of molecular diagnostic/assay platforms that can be used at common community events and can routinely screen female populations by simple and minimally invasive methods, such as a finger-prick test or a urine analysis. These methods should provide information to assist clinicians in making successful treatment decisions and increasing patient survival rate [9].

A range of biomarkers have been identified with different types of cancers. For cancer diagnosis multi-array sensors would be beneficial for multi-marker analysis [10]. More recently, synthetic (artificial) molecular recognition elements such as nanomaterials, aptamers, phage display peptides, binding proteins and synthetic peptides as well as metal oxides materials have been fabricated as affinity materials and used for analyte detection and analysis [11].

Nanotechnology approaches for cancerous cell destruction

A great progress has been made in the last 350 years, but the idea remains the same. If we see the cancerous cells of the tumour as the causing agents of the disease, then the obvious strategy is to remove or to destroy them. The most significant recent breakthroughs have been made in this area. A relatively long-standing strategy is to flood the body with substances that are especially toxic to tumour cells. Unfortunately, tumour cells are not dissimilar enough from healthy cells to distinguish one from the other using such large-scale techniques. A drug that is especially toxic to tumour cells is usually also toxic to healthy cells, and simply flooding the entire body with it causes system-wide damage and serious side effects. Almost everyone has heard of or seen chemotherapy patients who have lost their hair, lost significant weight, or developed other serious disorders & It is a common problem and in fact, we have also taken similar approaches to treating other seemingly incurable diseases such as AIDS and Hepatitis C, with similar results. A drug cocktail is a currently popular treatment for AIDS or a combination of several different

drugs, each some what effective against the disease. Administered together, these drugs can be effective, but taken constantly in large doses they can also be very damaging to the overall health of the patient. Two of the major drugs used to treat these diseases are Inteleukin-2 and Interferon, and some but not all of the side effects include a weakened immune system, loss of appetite, severe aches, pains, and flu-like symptoms, headaches, heart problems, stomach and digestive tract problems, eye problems, and hair loss, to list just a few [12,13].These alone have some experts furrowing their eyebrows, but in addition, many of these treatments have varying levels of psychological effects. While some patients are highly resistant and are lucky enough to get through the treatment with mild to moderate depression, others are plagued with severe depression, irritability, paranoia, insomnia, and even suicidal and homicidal tendencies. A select few are actually driven to suicide or homicide during or immediately after treatment. Yet the biggest setback is that these treatments are effective only some of the time, with the highest success rates ranging only from 25% to 75%. With such poor results, there is a pressing need for newer and more effective forms of treatment. While the subsequent discussion addresses research of treatments specific to cancer, nanotechnology does have the capability to deal with, both, AIDS and Hepatitis C as well as many other problematic conditions that currently have the medical community perplexed and frustrated [14]. Some recent works have explored cancer treatments from nanotechnology perspectives.

The nanoparticle method is simply the next step in the process of finding an effective way of administering Paclitaxel, which aside from these problems has a wide range of effective anti-cancer activity. In their work researchers took a similar approach to administering the drug preparation, in that they also injected the nanoparticle preparation into the tumor [15]. Successful development of biosensor-based cancer testing will require continued development and validation of biomarkers and development of ligands for those biomarkers, as well as continued development of sample preparation methods and multi-channel biosensors able to analyze many cancer markers simultaneously. The use of biosensors for cancer clinical testing may increase assay speed and flexibility, enable multitarget analyses and automation and reduced costs of diagnostic testing. Biosensors have the potential to deliver molecular testing to the community health care setting and to underserved populations. Cancer biomarkers identified from basic and clinical research, and from genomic and proteomic analyses must be validated. Ligands and probes for these markers can then be combined with

detectors to produce biosensors for cancer-related clinical testing. Point-of-care cancer testing requires integration and automation of the technology as well as development of appropriate sample preparation preparation methods [16]. Biosensor research and development over the past decades have demonstrated that it is still a relatively young technology. The rationale behind the slow and limited technology transfer could be attributed to cost considerations and some key technical barriers. Many of the more recent major advances had to await miniaturization technologies that are just becoming available through research in the electronic and optical solid state circuit industries.

Since our ultimate goal is to destroy the tumour, we realise that this can be achieved by limiting or eliminating the inputs of the needed nutrients and the useful energy that are vital to its growth and survival. Likewise, we can limit the outputs, which are necessary for the tumour cells to get rid of toxic waste products that are left over from the multitude of biochemical reactions continuously taking place. Furthermore, basic anatomy and biology tell us that cells within the human body get a vast majority of their nutrients and energy from the bloodstream, and likewise use the bloodstream to eliminate the toxins. Cells that are cut off from circulation quickly undergo necrosis and are effectively eliminated. Therefore, our goal is to separate the tumour from the circulation in order to kill it. Numerous studies have explored the possibility of isolating cancer tumours from the bloodstream [17]. The underlying principle of the study is that the cells within the growing tumour produce and send out basic Fibroblast Growth Factor (bFGF) accompanied by Vascular Endothelial Growth Factor (VEGF), the combination of which stimulates the development of new capillaries that grow into the tumour. The study used nanoparticles specifically designed to target cells that make up these freshly created capillaries by delivering to them ATPm-RAF, or pre-synthesised RNA (ribonucleic acid) strands responsible for inducing apoptosis. The nanoparticles consisted of a core of phospholipids, with the hydrophobic tails directed inward, which gave the outer surface of the particle a net negative charge. The charge allowed for facilitated conjugation of any desired DNA or RNA sequence to the particle's surface. Also imbedded in the core were integrin-antagonist lipids, whose tails were identical to the phospholipids tails, and whose heads served as the targeting moieties for the epithelial cells [14]. As a result of intravenous treatment with these nanoparticles in live mice, the newly formed capillaries were destroyed; cutting off the tumour from circulation and preventing further growth. The tumour cells

underwent necrosis and were eliminated shortly thereafter.

CONCLUSION

The application of nanotechnology in the field of cancer nanotechnology has experienced exponential growth in the Past few years. Nanotechnology offers innovative exposure of the destiny of medicine and surgery. With the advent and popularity of minimally invasive surgeries and interventional techniques, nanotechnology provides a future Platform for further development of drugs for cancer diagnosis. The multidisciplinary field of nanotechnology holds the promise of delivering a scientific breakthrough and may move very fast from concept to reality.

Table 1 Some examples of nanocarrier-based drugs on the market

Commercial name	**Type of nanoparticle/drug**	**Area of activity**
Abraxane®	Nanoparticulate albumin/paclitaxel	several cancers
Aurimune®	Colloidal gold/TNF	Solid tumors
Combidex®	Iron oxide nanoparticles	Tumor imaging
Cyclosert®	Cyclodextrin nanoparticles	Solid tumors
Doxil®	PEGylated liposomes/doxorubicin	Ovarian cancer
INGN-401®	Liposomal/FUS1	Lung cancer
Megace ES®	Nanocrystal/megestrol acetate	Breast cancer
SGT-53®	Liposome TF antibody/p53 gene	Solid tumors
Onco TCS®	Liposomes/vincristine	Relapsed aggressive non-Hodgkin's lymphoma

Table 2. New biosensors for several biomarkers.

Target/biomarker (biomarkers utilized for cancer detection)	**Disease**	**Biorecognition element**	**Transduction**
a-fetoprotein (AFP)	Cancer	Antibody Competitive assay Antibody Sandwich assay	Electrochemical (array) Electrochemical
BRCA1 gene	Breast cancer	DNA	Electrochemical
Cancer antigen 125 (CA 125)	Ovarian cancer	Antibody Competitive assay	Electrochemical (array)
Cancer antigen 15-3 (CA 15-3)	Breast cancer	Antibody Competitive assay	Electrochemical (array)
Cancer antigen 19-9 (CA 19-9)	Gastrointestinal tract	Carcinoma Antibody	Competitive assay Electrochemical (array)
Carcinoembryonic antigen (CEA)	Liver Cancer	Antibody Antibody Competitive assay	Competitive assay Electrochemical Direct assay (array) Electrochemical

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