

Nanotechnology in Cancer Diagnostics and Therapeutics

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Abstract. In each and every nation on the planet, cancer continues to be one of the main causes of mortality and a serious impediment to the advancement of efforts to extend the human lifespan. Now, the growth of nanotechnology has led to new ideas and approaches in the detection and treatment of cancer. These new ideas and methods were developed by researching and developing the one-of-a-kind features of materials at the nanoscale. In terms of detection and therapy, the effects that nanotechnology has had on cancer are discussed in this research, including the use of gold nanoparticles, electronic noses and gadolinium (III) oxide nanoparticles in diagnostic imaging as well as analysis of tumor-targeted therapies and nanoparticle drug transport, and concludes with a summary of the advantages and potential risks of nanoparticles. In general, nanotechnology has the potential to improve the sensitivity of detection methods, the accuracy of diagnostic results, and significantly boost treatment outcomes, thus opening up a new research avenue for the field of cancer science.

Keywords: Nanoparticles, cancer diagnosis, tumor targeting, EPR.

1. Introduction

Cancer is one of the main causes of mortality throughout the world, accounting for 13% of all fatalities and taking the lives of an estimated 7.6 million people every single year. By the year 2030, the number of deaths attributable to cancer is projected to reach 13.1 million [1]. There are three primary features that define cancer cells: first, there is a group of cells that are growing out of control; second, these cells infiltrate and destroy nearby tissues; and third, in certain instances, these cells travel to other areas of the body via the lymph and/or blood. Even though the field of oncology continues to develop treatment options in depth, cancer treatment remains a difficult challenge for the present. Cancer is not a single illness but numerous diseases, with each organ or system generating a separate set of disorders [2]. Although alterations in one's food and way of life can prevent the development of a few of cancers, the vast majority of cancers are not susceptible to such prevention and necessitate the development of new technologies in order to achieve better treatment results [3]. Chemotherapy, radiation therapy, and surgery are now the only three treatment options that are considered to be standard for cancer patients. On the other hand, the challenges that are frequently experienced with the treatments that are now available for cancer, such as inadequate concentrations of medications reaching the tumour and erroneous drug delivery to the target location, can result in catastrophic problems [4]. In addition to the fact that there is no test that can correctly diagnose cancer, which can only be evaluated by watching the patient's linked symptoms [5]. It takes a significant amount of time to conduct a comprehensive assessment of the patient and an in-depth investigation of his or her medical history; thus, when cancer is at last identified, this might create delays in the administration of following medicines. This also has a substantial influence on the percentage of cancer patients who are successfully treated. As a result, the development of nanotechnology has made it possible for researchers to access new tools for the diagnosis and treatment of cancer. Through advancements in imaging, nanotechnology not only boosts the proportion of patients who are diagnosed with cancer at an earlier stage, but it also makes it possible to improve the selectivity of medication targeting and the delivery efficiency.

The term "nanoscience" refers to the study of the distinct qualities possessed by materials with dimensions between 1 and 100 nanometers [4,5]. Nanomaterials, in contrast to conventional substances and systems, are regulated by the principles of quantum mechanics rather than the traditional laws of physics and chemistry. This is due to the fact that nanomaterials have a huge surface area to volume ratio. Because of these features, nanoparticles can exhibit exceptional optical, electrical, and magnetic capabilities at the nanoscale, which enables them to make significant contributions to a variety of sectors, including electronics and medicine. The integration of nanotechnology into medical practice is what is meant when people talk about nanomedicine. Nanomedicine mainly use nanotechnology to prevent, diagnose, monitor and cure disease. Nanotechnology also shows a lot of potential applications in the medical field. Some of these applications include imaging techniques and diagnostic tools, drug delivery systems, tissue engineering structures, implants, and drug therapies. These applications can provide more advanced treatments for a variety of conditions, including cardiovascular disease, cancer, and musculoskeletal disorders. For examples: micelles, which are primarily utilized as drug delivery agents, imaging agents, contrast agents, and therapeutic agents; liposomes, which are primarily utilized for drug delivery; dendrimers, which are utilized for imaging and drug delivery; carbon nanotubes, which are utilized as imaging contrast agents, biosensors, optical biosensors, and as drug delivery carriers; quantum dots, which may be used for medical imaging, drug administration, and cellular imaging [4]; metal nanoparticles, which can be used as imaging contrast agents; optical biosensors; and drug delivery carriers.

2. Diagnostic

To diagnose the cancer, large amount of methods have already been invented, and many detection of cancer today begin with a physical examination (CT or MRI) to detect any symptoms in patient's body. Then a biopsy may be taken for final detection of dubious tissues. This whole process may delay the therapy. Since when there is an obvious tumour in the body, the cancer has been serious to some extent. In addition, because of the radiation of CT and side effect of some contrast agent, injuries may be caused during the physical examination to human body. Therefore, there is urgent need for developments of novel detection with harmless, sensitive methods.

2.1. Application of gold nanoparticles (NPs) with thiolated oligonucleotide and fluorophore

According to Durkan C gold nanoparticles can be functionalized with thiolated oligonucleotide or a part of RNA of cancer cell to detect it [6]. The gold nanoparticles can combine with the RNA of the cancer which are attached to a fluorophore. Due to the proximity of fluorophore to gold nanoparticles, fluorescence is quenched. When thiolated oligonucleotide combines with complementary RNA, the fluorophore releases. Consequently, if there is cancer cell in blood or humor of patients, obvious fluorescence can be observed under a microscope. The benefits of this are obvious. First, since it detects cancer by detecting the biomarkers of cancer cell, it is more sensitive than traditional CT or MRI detection. In addition, compared with biopsy which might take days to wait for the result, it is time-saving. What is more, because of nano size of the particle, a gold NP only need to combined with several RNA, which made it easier to be manufactured [6]. Finally, it is harmless to human body, since it could not be injected into patients' body. However, this also is the limitation of this method. Because of the poor penetrability of fluorescence, it can only be used in vitro test. Therefore, fluorophore could not show which part of the body has tumor, unless the tumor is near the skin.

2.2. Cyrano-- the electronic nose

Cancer in lung and oral can be detected by Cyrano. It is a gas detection that detects biomarkers of cancer in a patients' breath. A Cyrano contains many cells, and each cell contains a transistor. The transistor consists of a block of silicon with a metal electrode which is called 'gate' on the top of it. The gate is functionalized with a molecular layer which can be the DNA of the cancer cell or any

complementary protein the biomarker of the cancer cell. If there are complementary biomarkers in the cell, the molecule on the gate will bind with the biomarkers, and the distribution of charge is changed, so that a voltage is applied on the gate. Mentioned by Durkan C, the current drop flowing underneath the 'gate' can be controlled by applying a voltage onto the gate [6]. As a result, when the biomarkers attach to the protein on the gate, a significant drop appear in the current underneath. In addition, the concentration of the biomarkers in the patient's breath can be determined by the amount of current drop, which is an extra information. Due to the functionalization of transistor with molecular layer which is in nanoscale, the author considers the electronic nose as an application of nanotechnology. Compared with traditional physical examination, using Cyrano has benefits. First, as there is not anything getting into patient's body, it is harmless to patient's health. Additionally, according to R. Thirumani *et al.* with LDA, Cyrano can detect and distinguish the volatile organic compounds which might be used as biomarkers, released by different types of cancer cell in an accuracy of 100% [7]. However, since it can only test the breath, it only is able to detect cancer in lung and respiratory tract.

2.3. MRI and gadolinium (III) oxide (Gd₂O₃) nanoparticles (NPs) with silicon-based nanocomposite polymer

2.3.1. MRI

MRI is a powerful tool to detect illness. It diagnoses illness based on the principle of nuclear magnetic resonance. Compared with other diagnostic methods, MRI has a high resolution of image. Additionally, because of the absence of radiation, it is harmless to human body. However, according to Mortezaadeh, T. *et al.*, due to the negligible difference between the number of atoms in low-energy state and high-energy state, MRI has a main drawback--low sensitivity [8]. To overcome this, many contrast agents have been launched, and Gd-based compounds, which mainly consist of central Gd³⁺ ion complexes with chelating ligand, is the most widely used contrast agent in clinical research [8]. Nevertheless, Mortezaadeh, T. *et al.* complain that because of the release of Gd³⁺, these contrast agents could cause serious side effects to human body, such as nephrogenic systemic fibrosis and long-term deposition in brain tissue [8]. Hence new contrast agent is in demand.

2.3.2. Gadolinium-nanocomposite polymer emulsion (Gd-NCPE)

Gd-NCPE is one kind of MRI contrast agents, which are consisted of gadolinium (III) oxide (Gd₂O₃) NP covered with a siliconbased nanocomposite polymer. Compared with common Gd-based contrast agent such as Magnevist, Gd-NCPE has much higher incremental relaxivity because of the Gd₂O₃ NP core [9]. In addition, due to its nanosize, it is a potential contrast agent that can used in cell tracking in MRI, and Gd based nanoparticle might enhance the sensitivity of MRI in a significant extent to realize cellular and subcellular imaging [9].

Riyahi-Alam, N. *et al.* has tested the toxicity of Gd-NCPE to human cell by detecting LDH activity, which is proportional to the amount of dead cells [9]. As a result, the leakage of LDH in each group shows that the plasma membrane is not affected by Gd-NCPE at any concentration. Therefore, the Cytotoxicity of Gd-NCPE incremental relaxivity is negligible. However, this examination is still not enough to make a conclusion on whether it is harmful to human body and more experiments are needed. What is more, researchers also detected the signal intensity of Gd-NCPE [9]. The result shows that the when the concentration is lower than about 1.5 mM, the signal intensity of Gd-POSS is higher than that of Gd-DTPA, and at about 1.25 mM the signal intensity of Gd-POSS has a highest value [9]. Overall, the Gd-NCPE has a good signal intensity for low concentration compared to other MRI Gd-based contrast agent. The authors think it might mean this contrast agent has a potential to replace the traditional contrast agent, since it need a less amount to reach a same or even higher signal intensity, which means it is more economic efficient and can reduce some potential negative effects caused by it to human body.

3. Therapeutics

In the treatment of cancer, chemotherapy has been used mainly to treat malignant tumors so far. However, there is a serious problem with cancer chemotherapy; when the dose of the drug used is equal to the dose used to eradicate cancer cells, the chemotherapeutic approach not only causes damage to cancer cells, but also causes irreversible damage to normal tissues due to its excessive drug dose. Therefore, drugs with nanocarriers can selectively attack cancer cells, and this treatment option can significantly increase the effectiveness of the treatment and reduce its toxicity to the body. Nanotechnology is now being utilized as a mechanism for pharmaceutical administration due to the extremely small molecular structure it possesses. Utilization of nanocarriers, such as liposomes, micelles, dendritic macromolecules, quantum dots, and carbon nanotubes, in a significant and widespread manner in the treatment of cancer.

3.1. Tumor targeting

The ability to specifically target cancerous tumours is one of the possible basic benefits of cancer treatment. When used as carriers, nanoparticles (NPs) will result in a significant improvement in the specificity of tumour targeting. The separation of non-malignant cells from cancerous cells as well as the targeted killing of cancerous cells in a selective manner using either active or passive targeting strategies are at the heart of this nanotechnology objective. Enhanced permeability and retention (EPR) effects are utilized in the process of passive targeting in order to boost the concentration of nanoparticles within tumours. In human tissues, blood vessels in normal tissues should seem to be smooth and without gaps, however blood vessels in tumour tissues have very tiny gaps ranging from 600 to 800 nm. The EPR effect is a phenomenon that describes how nanoparticles are able to slip across these gaps and concentrate in the tissue of a tumour. For instance, gold nanorods that have been transported to tumour tissue by means of EPR can cause the tumour to get heated, and then the laser can cause it to burn [10]. The efficacy of EPR is contingent not only on factors like as the size of the tumour, the kind of the tumour, and the degree of heterogeneity in the tumour, but also, and most crucially, on the intensity of the targeted therapy.

Active targeting refers to the use of selective molecular recognition of antigens expressed on the surface of tumour cells or the targeting of NPs to malignant cells using biochemical properties associated with malignancy. Active targeting can be accomplished by either using antigens expressed on the surface of tumour cells or targeting NPs to malignant cells using biochemical properties. However, achieving this aspect of the goal in clinical trials is still challenging and currently mainly depends on the EPR effect. One possible option would be to affix a variety of ligands to nanocarriers through ligand-receptor or antibody-antigen interactions. These ligands have the ability to selectively bind to receptors that are located on the surface of tumour cells, which causes the drug to be released into certain environments. These environments can be characterized by factors such as the pH of the surrounding environment, the enzymes that are present, and the ion concentrations. Both active and passive methods of localisation can be employed on their own or in conjunction with one another to achieve the same results. Both approaches can benefit from surface changes of NPs that reduce the amount of absorption by the macrophage phagocytic system (MPS) and, as a result, increase the amount of time that the particles are in circulation [10].

3.2. Drug delivery

In addition, whereas the accumulation of NPs in tumour tissues requires a long circulation time, the nanoparticles must be able to remain in the bloodstream for a considerable amount of time without being removed by absorption through the reticuloendothelial system (RES) in order for them to be able to reach the target tumour tissue. In addition to this need, the nanocarriers should be able to prevent the degradation of the medicine. This is due to the fact that during circulation, nanoparticles that have not undergone any surface changes are often collected by the MPS [10]. Nanoparticles can have hydrophilic polymers applied to their surfaces so that they can be coated to overcome this

problem. An illustration of this would be coating the outside of the NPs with polyethylene glycol, which lowers the affinity of the proteins involved in the mating of the NPs and lowers the absorption of MPS [4]. Because of the presence of polyethylene glycol (PEG), the immune system of the body is prevented from recognizing the nanoparticles as foreign bodies. "PEGylation" refers to the technique of covalently attaching polyethylene glycol (PEG) to a specific molecule and is currently considered a common practice in the field of targeted pharmaceutical delivery systems. PEG can be attached to a molecule by either chemical or electrostatic means. Anti-cancer therapy has benefited significantly from the invention of polyethylene glycol (PEG) drug delivery systems. This paves the way for the nanoparticles to continue their journey through the bloodstream and eventually arrive at the tumour. Polyethylene glycols have the ability to protect proteins, enzymes, small molecule drugs, liposomes, and nanoparticles from a variety of tissue or intracellular degradation mechanisms, which in turn increases their retention time, thereby increasing their therapeutic potential [10]. PEGylation has successfully changed the pharmacokinetics (PK) of a large number of drugs and significantly improved the pharmacological value of those drugs; its most recent developments include the production of stimuli-sensitive polymers/smart polymers and polymeric micelles that respond to the pathophysiological environment of the target site with fewer toxic side effects and increased efficacy.

4. Discussion

4.1. Advantages

Throughout previous developments in diagnostic and therapy of cancer, nanomedicine is significant. The functionalizing of particles or materials with certain biomarkers of cancer cell such as the RNA of cancer cell can be considered as an application of nanomedicine, because the size of these biomarkers and corresponding receptor is in nanoscale. What is more, nanomedicine also realizes the targeting of cancer. Due to the application of functionalization, the active targeting is possible, while using nanoparticle with EPR could also target the tumour. Additionally, in the application of AuNPs with thiolated oligonucleotide and fluorophore, the NPs reduce the number of RNA segment that particles need to be functionalized with, so the process of functionalization is easier. According to Mortezaadeh, T. et al., selection of a proper coating material can reduce the toxicity of the Gd-based contrast agent [8]. Therefore, the negligible cytotoxicity of Gd₂O₃ POSS MRI contrast agent might be attributed to the application of a 'silica nanocomposite: polyhedral oligomeric silsesquioxane-poly (carbonate-urea) urethane (POSS-PCU) [9].

4.2. Potential risks

As a result of the proliferation of nanotechnology, there has been an uptick in interest in the subject among the general public. Concurrently, however, questions regarding the technology's safety and the possible hazards it may provide have also been raised. The possible dangers posed by nanotechnology may be broken down into three categories: health hazards, environmental concerns, and societal problems. The possible dangers that might be caused by nanotechnology are broken down into categories and listed in Table 1 below.

According to a number of studies, nanoparticles with a limited solubility can provide a greater risk of harm and toxicity [11]. Explosive and catalytic impacts are two other examples of the possible dangers offered by nanoparticles. It is essential to keep in mind that only some nanomaterials are regarded as being potentially hazardous, in particular those that are reactive and highly mobile. The sheer existence of nanomaterials in laboratory conditions does not constitute a hazard to humans and the environment until the results of more comprehensive investigations can be confirmed [12].

Table 1. Potential Risks of Nanotechnology

Area	Potential Risk
Health	<ol style="list-style-type: none"> 1. Nanoparticles can be absorbed through the skin or infiltrated into the body by the injection route during medical procedures. 2. Nanoparticles that enter the body may be able to cross the blood-brain barrier due to their high mobility. 3. Nanoparticles can overload phagocytes, which can affect the body's immune system 4. Nanoparticles may influence physiological or biological processes in the body.
Environment	<ol style="list-style-type: none"> 1. Synthetic nanoparticles require high energy. 2. The recovery rate of nanoparticles is low. 3. Some nanoparticles may contain substances that are toxic to the environment and cause environmental hazards.
Society	<ol style="list-style-type: none"> 1. Nanoparticles are costly to build. 2. Nanoparticles may be used in military applications. 3. Nanotechnology may be controlled and monopolized by 4. large companies.

5. Conclusion

Cancer has become one of major causes of death around the world nowadays. To reduce its harmfulness and improve the cure rate of it, developments in both cancer detection and therapy are consumed. This paper discusses different developments and methods in cancer diagnostic and therapy that apply nanomedicine. Throughout these developments, nanomedicine brings several advantages. Its application reduces the cytotoxicity of Gd-based MRI contrast agent, makes different method of cancer targeting possible, maximizes the circulation time of drugs, and prevents the degradation and leakage of the drug or contrast agent covered with a layer of nanomaterials. However, before the launch of nanomedicine, the potential risks of it are still needed to be considered, such as its toxicity, explosive effect, catalytic effect, and the effect after entering nature environment. The development of new detection and therapy should improve the welfare and the rate of cure of patients, instead of causing more potential risks and problems.

References

- [1] Barnard RJ. Prevention of cancer through lifestyle changes. *Evid. Based Complementary Altern. Med.* 2004, 1, 233 – 239.
- [2] Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. *Semin. Radiat. Oncol.* 2007, 17, 2 – 9.
- [3] Watabe K, Nishi M, Miyake H, Hirata K. Lifestyle and gastric cancer: a case-control study. *Oncol. Rep.* 1998, 5, 1191 – 1194.
- [4] Sim S, Wong NK. Nanotechnology and its use in imaging and drug delivery (Review). *Biomed Rep.* 2021 May; 14 (5): 42.
- [5] Diagnosis. Stanford Health Care (SHC) - Stanford Medical Center. (2018, March 15). Retrieved November 13, 2022, from <https://stanfordhealthcare.org/medical-conditions/cancer/cancer/cancer-diagnosis.html>.
- [6] Colm Durkan, Session I-4, United Kingdom, online video, accessed 15 October 2022. https://us02web.zoom.us/rec/share/ZluwWCzkkjA0C6syXCsmQhcKFNp_IQ2kthOdkLV7OLy1w9oQ2lq-x9swMUyZn6nH.wSWawOW3hEaPPHu5.
- [7] Thriumani, R., Zakaria, A., Hashim, Y.Z.HY. et al. A study on volatile organic compounds emitted by in-vitro lung cancer cultured cells using gas sensor array and SPME-GCMS. *BMC Cancer* 18, 362 (2018).
- [8] Mortezaadeh, T., Gholibegloo, E., Alam, N.R. et al. Gadolinium (III) oxide nanoparticles coated with folic acid-functionalized poly (β -cyclodextrin-co-pentetic acid) as a biocompatible targeted nano-contrast agent for cancer diagnostic: in vitro and in vivo studies. *Magn Reson Mater Phy* 32, 487 – 500 (2019).

- [9] Riyahi-Alam, N., Behrouzkoa, Z., Seifalian, A. et al. Properties Evaluation of a New MRI Contrast Agent Based on Gd-Loaded Nanoparticles. *Biol Trace Elem Res* 137, 324 – 334 (2010).
- [10] Gmeiner, W. & Ghosh, S. (2014). Nanotechnology for cancer treatment. *Nanotechnology Reviews*, 3 (2), 111 - 122.
- [11] Sahaym U, Norton M. Advances in the application of nanotechnology in enabling a hydrogen economy. *J Mater Sci*. 2008; 43: 5395 – 5429.
- [12] Rickerby DG, Morrison M. Nanotechnology and the environment: A European perspective. *Sci Technol Adv Mater*. 2007; 8: 19 – 24.