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CLINICAL APPLICATIONS OF NANOROBOTS IN CANCER DIAGNOSIS AND THERAPY: CURRENT PROGRESS AND FUTURE PROSPECTS

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ABSTRACT

Cancer is a major health issue worldwide, and the need for advanced diagnostic and therapeutic techniques is critical to improve patient outcomes. Nanorobots offer a promising technology for cancer diagnosis and therapy, as they can be programmed to target cancer cells specifically and deliver drugs or other agents directly to the tumor site. This paper provides an overview of the current status and future prospects of nanorobots in cancer diagnosis and therapy. We first discuss the various types of nanorobots that have been developed, including DNA, protein-based, and hybrid nanorobots. We describe how these nanorobots can be designed to recognize and target cancer cells based on their molecular signatures. We then review the current applications of nanorobots in cancer diagnosis, including their use in detecting cancer biomarkers and imaging cancer cells. We also highlight how nanorobots can be utilized to enhance the accuracy of cancer diagnosis by providing real-time feedback during diagnostic procedures. Finally, we discuss the current applications of nanorobots in cancer therapy, such as drug delivery and photothermal therapy. We explain how nanorobots can be engineered to release drugs or other agents specifically at the tumor site, minimizing side effects and toxicity. We also demonstrate how nanorobots can be used to deliver photothermal agents to cancer cells, allowing for the selective destruction of tumor tissue. In summary, nanorobots have the potential to revolutionize cancer diagnosis and therapy. Although challenges remain, such as improving the safety and efficiency of these technologies, the prospects of nanorobots in the fight against cancer are considerable.

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Introduction

Cancer is a devastating illness that affects people of all backgrounds, regardless of their age or socioeconomic status. The term "cancer" was first used by Hippocrates, who believed that an excess of black bile was the cause of the disease. Although this theory has been discredited, the name for the condition remains the same. [1]

Nanotechnology refers to any technology that operates on a microscopic scale and has practical applications. It encompasses the study of physical, chemical, and biological systems at the atomic and molecular levels, as well as the integration of nanoparticles into larger systems. In recent years, nanotechnology has become a significant driving force in various sectors, including manufacturing, healthcare, energy, biotechnology, and national security. Many researchers believe that nanotechnology will be the next major industrial revolution, comparable to the impact of semiconductors, information technology, and molecular biology. [2]

Advances in nanotechnology research have led to the discovery of new materials, processes, and phenomena at the nanoscale. These developments have opened up fresh opportunities for the creation of innovative nano systems and nanostructured materials. The properties of materials at the nanoscale can differ significantly from those at larger scales. As the size of a material decreases, small changes in properties occur until, at sizes below 100 nm, dramatic changes can occur. Nanostructures that have one, two, or three dimensions in the nanoscale range are referred to as quantum wells, quantum wires, and quantum dots, respectively. The term "quantum" is used because the changes in properties arise from the quantum-mechanical nature of physics in the ultrasmall domain. The ability to nanostructure materials offers exciting new possibilities for developing novel materials and enhancing their performance. [2]

NANOTECHNOLOGY IN CANCER TREATMENT

Cancer remains a significant contributor to mortality rates in the United States, and its global incidence continues to rise. At present, the primary approach to treating cancer involves surgical removal of the tumor, followed by a combination of chemotherapy and radiation. However, these therapies face numerous obstacles, including indiscriminate systemic distribution of anti-cancer agents, inadequate drug concentrations reaching the tumor, and limited capacity to track therapeutic efficacy. Insufficient delivery of drugs to the intended location often results in multiple complications, such as resistance to multiple drugs.[3]

Enhancing targeting specificity and improving delivery efficiency are the primary objectives in the advancement of therapeutic agents and imaging contrast formulations. Ideally, a therapeutic drug would accumulate predominantly in tumor lesions while sparing normal tissues from damage. To achieve this goal, a rational approach involves linking therapeutic drugs to mAbs (monoclonal antibodies) or other ligands that specifically bind to antigens or receptors that are frequently or exclusively present on the surface of tumor cells. [4-6]

Nanotechnology has opened up new avenues for cancer diagnosis and treatment. With the help of nanoscale devices, scientists can now attach various functional molecules to them, including tumor-specific ligands, antibodies, imaging probes, and anticancer drugs. As these devices are

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much smaller than cancer cells, they can easily travel through the leaky blood vessels and interact with targeted proteins on both the surface and inside of cancer cells. Consequently, these nanodevices can serve as precise vehicles to deliver drugs to cancer cells while minimizing the adverse effects of treatments. These advancements in nanotechnology can significantly improve the effectiveness of cancer therapeutics and imaging.

The Interdisciplinary fields of engineering, chemistry, and medicine have contributed to the development of a broad range of nanoparticles for molecular imaging and targeted therapy in cancer nanotechnology. These nanoparticles have diverse designs and applications, offering potential solutions to several current challenges in cancer treatments. By utilizing such advanced nanotechnology, cancer therapies can become more effective and efficient in addressing the various obstacles associated with cancer treatment. [7-10]

Nanorobots and their types

Nanorobots are tiny machines that possess comparable capabilities to their larger counterparts and have a wide range of applications in medicine, industry, and energy conservation. They can be employed in developing nanomotors and addressing infertility concerns by enhancing sperm motility when attached to them. The versatile nature of nanorobots makes them a valuable asset in several fields and industries.[11]

Bio-nanorobots, which are a type of organic nanorobot, are created by merging virus and bacterium DNA cells, and are commonly studied alongside inorganic nanorobots. Inorganic nanobots are created using synthetic proteins, diamond structures, and other materials, and are generally more hazardous than organic nanobots. However, researchers have devised a method to encapsulate the nanobots, reducing the risk of toxicity and destruction by the body's natural defence mechanism. This method has the potential to enhance the safety and effectiveness of inorganic nanobots. [12-14]

By examining the biological motors found in living cells, scientists can gain insight into how to power micro and nano-sized devices using reactive processes. The Chemistry Institute of the Federal Fluminense University has developed a natural nano valve composed of silica (SiO2), beta-cyclodextrins, and organo-metallic molecules. The valve consists of a tank covered with a shutter that houses dye molecules and releases them in a uniform manner when opened. This device has potential therapeutic applications. [15-18]

In certain studies, proteins are used to fuel nanomotors capable of moving large objects, and DNA hybridisation and antibody proteins are employed in the creation of nanorobots. Nanorobots can be functionalized using various chemical compounds and have been investigated in nanomedicine, particularly in the development of targeted drug delivery systems (DDS). These DDS devices can deliver medications to specific locations in the body while adjusting the dose and release amount. This technology has potential applications in treating joint disorders, dental issues, diabetes, hepatitis, cancer, and other ailments. [19]

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This technology offers the advantage of diagnosing and treating diseases with minimal impact on healthy tissues, reducing the chances of adverse effects and enabling precise cellular and sub-cellular level healing and remodeling therapy. [20]

Chemotherapy drug delivery using nanorobots in cancer treatment

Recent developments in medication delivery have led to improved precision in delivering drugs to specific targets, utilizing nanosensors that can detect specific cells and control drug release through the use of smart medicines.[19] Chemotherapy drugs traditionally work by targeting rapidly dividing cells, a hallmark feature of cancer cells. However, their therapeutic scope is often limited, leading to toxicity towards normal fast-replicating stem cells, such as those in bone marrow, the gastrointestinal tract, macrophages, and hair follicles. These side effects can cause myelosuppression, mucositis, alopecia, organ dysfunction, thrombocytopenia, anemia, and other hematological complications. To reduce its toxicity, doxorubicin is often used in combination with other anti-cancer drugs to treat various types of cancer, including Hodgkin's disease. Paclitaxel, an intravenously administered drug, is utilized for the treatment of breast cancer, but it can cause notable side effects such as bone marrow suppression and gradual neurotoxicity. Cisplatin, an alkylating agent that induces intra-DNA binding, may result in adverse effects such as dizziness, severe vomiting, and potential nephrotoxicity. [21] Camptothecin is used to treat cancer by targeting type 1 topoisomerases, an enzyme crucial for the replication of genetic material in cells. Several efforts have been made to utilize nanotechnology to develop drug delivery systems (DDS) that can mitigate the adverse effects of conventional treatments. One such approach involves coating single-walled carbon nanotubes (SWNTs) with doxorubicin.[22] In the treatment of metastatic tumor cells, doxorubicin was incorporated into a hybrid of collagen and polymer prodrug. The use of polymeric prodrug nanotechnology is an innovative advancement in targeting rapidly dividing abnormal cells. Nanotechnology is constantly exploring biocompatible materials for developing drug delivery systems (DDS). Hydroxyapatite (HA) nanoparticles, a crucial component of bones and teeth, have been utilized to deliver paclitaxel, an anti-cancer drug, with findings suggesting that hydrophobic drugs should be administered as the initial therapy. [23] Numerous efforts have been made to develop drug delivery systems (DDS) using nanotechnology, which can minimize the harmful effects of conventional chemotherapy. The drawback of traditional chemotherapeutic drugs is their inability to selectively target cancerous cells, leading to adverse effects that may necessitate treatment delays, reduced dosage, or temporary discontinuation. With the ability to navigate as blood-borne devices, nanorobots have the potential to assist in essential therapeutic procedures, including early diagnosis and precise drug administration. [24] Nanorobots can assist in administering chemotherapy in a smarter way, by selectively targeting cancerous cells and tissues, while avoiding damage to healthy surrounding cells from the toxicity of the drugs being used. By acting as drug transporters, nanorobots can also ensure timely and sustained doses of chemotherapy drugs, with the desired pharmacokinetic properties for effective anti-cancer therapies. [25].

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Nanorobots can be utilized in clinical applications such as diagnosis, therapy, and surgery by administering them intravenously. The nanorobots are injected into the recipient's bloodstream and can be used to perform tasks such as targeted drug delivery or tissue repair. The pharmacokinetics of chemotherapy involves the uptake, metabolism, and excretion of drugs, as well as a period of recovery to allow the body to recuperate before the next chemotherapy session. For small tumors, patients may undergo treatment in cycles lasting two weeks. [38]. Nanorobots can be utilized as an initial screening tool in medicine, allowing for rapid assessment and diagnosis of tumors using proteomic-based sensors. The uptake kinetics of contrast agents during magnetic resonance imaging can predict the delivery of protein-based drugs to solid tumors with very low molecular weights. Testing and diagnostics are crucial components of nanorobotics research, offering speedy diagnoses during the initial visit and eliminating the need for follow-up appointments after lab results, thus enabling the identification of illnesses at an earlier stage. However, the energy required for propulsion presents a significant limitation to the use of nanorobots in vivo, as their small size and strong viscous forces lead to reduced productivity and convective motion, necessitating greater energy expenditure. The effectiveness of a medication administered through nanorobots for targeted delivery depends on its retention within the tumour after passing through cellular membranes. The pathways through which the medication is transported from the bloodstream to the tissue can also affect the success of chemotherapy in treating the tumour, with the medication's structure playing a key role in this process. By optimizing these pathways, more effective tumour chemotherapy can be achieved. [26-28] Recent research suggests that nanotechnology and DNA-based molecular-scale devices show great promise in advancing the field of nanomedicine by offering superior control over shape and site-specific functionalization. However, despite these benefits, uncertainties associated with the biological environment and the risk of immune activation remain significant barriers to the in vivo deployment of these technologies. One potential application of nanorobots in cancer medicine is the reduction of chemotherapeutic side effects. To achieve this goal, nanorobots designed using a combination of carbon nanotubes and DNA have emerged as leading contenders for the next generation of nanoelectronics.[30] The development of a compound bio-sensor utilizing single-chain antigen-binding proteins is made possible through the use of complementary metal oxide semiconductor (CMOS) technology to build circuits with characteristic sizes in the tens of nanometers. This approach enables targeted drug release through the use of proteomics and bioelectronics signals to stimulate nanoactuators. The nanorobot is capable of detecting predetermined modifications in protein gradients and adjusting medication delivery accordingly. [31] The Identification of significant medical targets is directly connected to thermal and chemical signal changes. Under diseased conditions, certain proteins, such as Nitric oxide synthase (NOS), E-cadherin, and B cell lymphoma-2 (Bcl-2), may exhibit fluctuating aggregation near these targets. In addition, tissues with inflammation often experience changes in temperature. A framework that considers both chemical and thermal characteristics is essential for the clinical and therapeutic evaluation of nanorobot templates. Furthermore, such characteristics play a crucial role in the diagnostic and therapeutic

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recommendations for evaluating nanorobot frameworks. To provide a viable model for nanorobots operating within the body, a three-dimensional real-time simulation is used. One significant breakthrough involves the development of a hardware structure based on nano-bioelectronics that allows for the use of nanorobots in neoplasia therapy. [32]

The ongoing efforts to create medical micro-robots have resulted in the development of a full medical nanorobot, known as "Respirocytes," which has been detailed in a peer-reviewed publication. Respirocytes are theoretical mechanical red blood cells made up of 18 billion perfectly ordered atoms. These nanobots are capable of delivering 236 times more oxygen per unit volume to the tissues and cells of the body than normal red blood cells. Another type of nanobot, called microbivores, can monitor the circulation of the body and detect and eliminate pathogens like bacteria, viruses, or fungi. These nanobots use up to 200 pW of power and operate up to 1,000 times faster than natural biological defenses. They can break down germs and eliminate even the most serious septicaemic diseases within a short period. The waste produced by microbivores is harmless sugars and amino acids, which eliminates the possibility of sepsis or septic shock. [33].

CONSTRUCTION OF NANOBOTS

A group of researchers including Bachelet, have created nanobots comprised of DNA that serve as a transport mechanism for drugs used to treat cancer. These nanobots can specifically target and eliminate cancer cells once injected into the body. The nanobots are significantly smaller than red blood cells by a factor of 200 and have a diameter of just 35 nm. To construct the nanobots, CAD nano, an open-source software, was used to design their structure, and DNA origami was utilized to physically build them. DNA origami is a technique that allows for the creation of small structures with precise shapes using DNA. [34]. Through the use of a staple strand and a longer strand, DNA can be manipulated into a specific shape by binding the two together via complementary base pairs. Figure below outlines the process of designing and constructing these nanobots, which resemble an open-ended barrel consisting of two halves that can be opened and closed like a clamshell. These halves are held together by molecular hinges and locks made of DNA double helixes. Inside the nanobots, there are 12 sites available for attaching payload molecules, while outside there are two locations for attaching aptamers, which are short nucleotide strands with specialized sequences for identifying target molecules on a cell. The drug is stored within the nanobot and secured by molecular anchors. The aptamers act as clasps, and once they locate their target, the nanobot opens up, allowing the payload to be released. [35]

The nanobots have been designed to operate in two distinct states: ON and OFF. When they encounter a target cell through the identification of its surface proteins, they divide into two halves, allowing the drug to be administered solely to that specific cell (in the ON state). Conversely, in the OFF state, the nanobots remain closed and navigate past healthy cells without interfering with them. [36]

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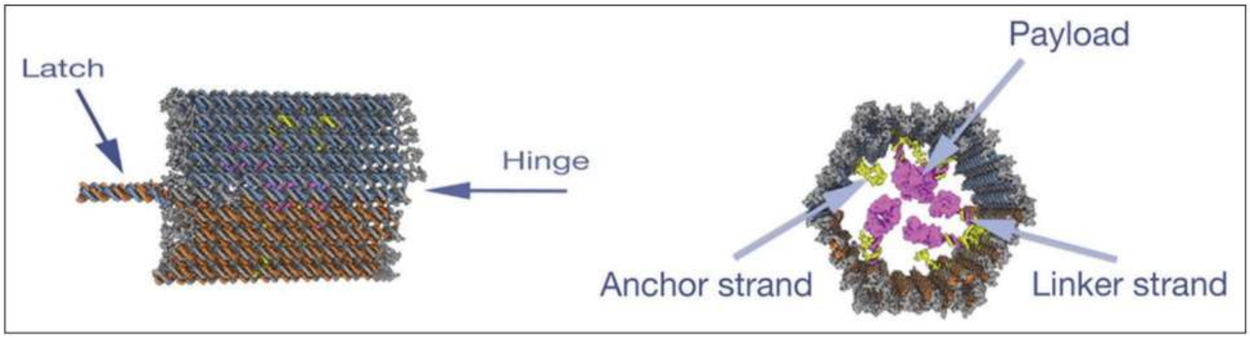

Fig. 1: Construction of the nanorobot

WORKING METHODOLOGY OF NANOBOTS

An aptamer-encoded logic gate regulates the behavior of the nanobots. With the aid of DNA, nanoparticles can be transformed into self-contained biocomputing structures that are capable of performing Boolean logic gates such as NAND, NOT, AND, and OR. As DNA is a well-suited substrate for computing, it has been utilized in various logic circuits and robotics. The DNA contains the logic gating function, which is activated by the disassembly of its structures in response to input signals. [37] Various forms of DNA-based biocomputing have been successfully demonstrated. A recent breakthrough involves the utilization of DNA origami to create nanoscale robots capable of dynamic interactions with each other inside the human body. These interactions generate logical outputs that determine whether the nanobots release drugs by switching between the ON and OFF states when they detect the target cell. Figure below illustrates the two distinct positions of the nanobots. [38]

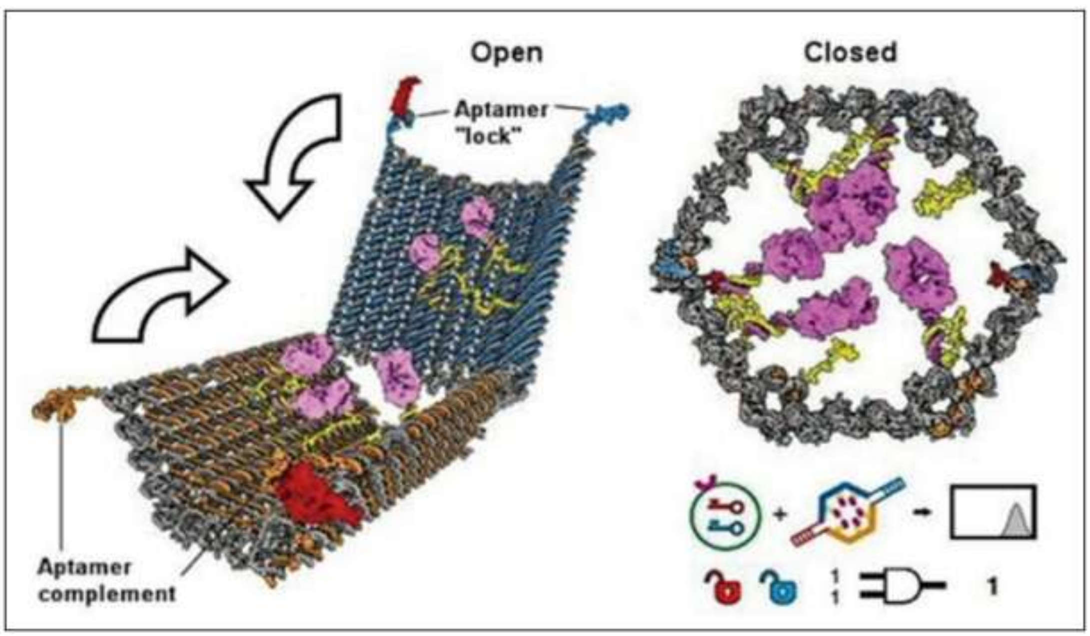

Fig. 2: On and off position [60]

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ADVANTAGES OF NANOBOTS

The primary advantages of nanobots are their speed and durability, particularly in drug delivery applications, which offer several benefits over current methods. Nanobots provide controlled and accurate release of drugs with minimal side effects, reducing the possibility of surgeon error. Additionally, computer-controlled drug delivery and faster drug action are among their key strengths. [34].

DISADVANTAGES OF NANOBOTS

Designing nanobots is an expensive and complicated process, and more research is needed to ensure they can evade the body's immune response. There is a potential risk of nanobots being misused as bio-weapons by terrorists, which could pose a threat to society. Additionally, like nanobacteria, foreign nanobots may have harmful effects on the body. Therefore, precautions must be taken to address this concern, as relying too heavily on nanotechnology could challenge our immune systems. Furthermore, if nanobots were to self-replicate, a harmful variant could be produced. [35, 36].

CONCLUSION

The objective of this review is to provide an overview of the technological advancements in nanotechnology and its potential application in medicine, particularly in the form of nanorobots for drug delivery in cancer treatment. Cancer, a condition characterized by uncontrolled growth and spread of malignant cells in the body, continues to affect a growing number of individuals each year. Nanorobotics has emerged as a promising field in cancer treatment, offering a range of therapeutic options to improve patient outcomes. Key factors for successful cancer treatment include timely diagnosis and management, as well as reducing the side effects of chemotherapy. Programmable nanorobotic devices that operate at the cellular and molecular level can enable precise and targeted treatment, while minimizing adverse effects. Furthermore, nanorobotics holds potential in resolving cellular damage caused by irreversible mechanisms, reversing atherosclerosis, enhancing the immune system, modifying DNA sequences, improving respiratory function, and achieving rapid treatment outcomes.

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