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Nanobots: The Future of Targeted Drug Delivery and Cancer Treatment

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Abstract

Cancer is still one of the top causes of deaths in the world, taking almost 10 million human lives in 2020. While great strides are being made in the management of this disease, traditional tumour treatments still grapple with immense systemic toxicity, drug resistance, and the failure of drugs to precisely target complex tumour environments. Nanotechnology may overcome these issues, and a nanostructure robot for targeting drug delivery nanobots is increasingly considered one of the groundbreaking approaches in oncology. The present review covers the development, mechanisms, and applications of nanobots in cancer therapy, focusing on their potential to improve treatment efficacy with reduced adverse effects. Smart, stimuli-responsive nanobots can release their content based on tumour-specific factors like pH or temperature, enhancing therapy precision. Applications range from immunotherapy and gene therapy to overcoming obstacles in the form of the blood-brain barrier, demonstrating the versatility of nanobots in the treatment of aggressive cancers. More recently, AI and organ-on-a-chip models are combined to further perfect the design of nanobots and forecast the results of therapeutics, moving toward personalized treatments of cancer. Challenges are yet incomplete: biocompatibility, immunogenicity, and scalability remain relevant, besides regulatory and ethical concerns. Overcoming such limitations requires both interdisciplinary collaboration and technical development. The present review underlines the transformative potential of nanobots in the field of drug targeting and cancer therapy, a position whereby nanobots are a cornerstone of next-generation precision medicine. Nanobots overcome current limitations, hence promising safer, more effective, and personalized solutions for cancer treatment.

Keywords: cancer treatment, diagnostics, drug delivery, immunotherapy, nanobots.

INTRODUCTION

In 2020, nearly 10 million deaths occurred from cancer, a factor that makes it rank as the second leading cause of death in the world, hence a major public health concern. Fundamentally, cancer arises when genetic mutations and epigenetic modifications upset the body's regular cellular processes. These changes allow for the development and multiplication of aberrant cells unchecked, enabling them to make blood vessels, resist natural cell death, increase growth signals, and invade adjacent organs.[1] Cancer is one of the most complex diseases to understand and treat. It presents major challenges to diagnosis, treatment, and management on account of more than 200 distinct types and subtypes.[2] Cancer develops from several variables like genetic susceptibility, environmental exposures, and lifestyle decisions related to smoking, drinking, and poorly eating. Efforts are also being hindered by the presence of persistent infections, such as *Helicobacter pylori* and human papillomavirus, which have been linked to cancer [3].

Even now, the conventional treatments of radiation, chemotherapy, and surgery are in wide use despite their serious disadvantages. Surgery is effective in the removal of small, localized tumours. However, it is often inappropriate for diffuse cancers or those in inaccessible locations.[4] Chemotherapy and radiation, though designed to target rapidly proliferating cancer cells, can cause injury to normal organs. This may result in serious adverse consequences, such as compromised immunity, systemic toxicity, and a reduced quality of life for patients.[5] Moreover, certain treatments present multidrug resistance and fail to penetrate deep inside the tumour microenvironment, events that may lead to incomplete eradication of cancerous cells with a consequent increase in recurrence rates. The search for new treatments has opened a window of interest in nanotechnology. One promising strategy in precision oncology under exploration is monopolization.[6]

Nanotechnology has changed many fields, including medicine, by offering innovative answers to difficult medical issues. Among these developments, nanobots have shown great promise in the delivery of drugs with accuracy for the treatment of cancer. [7] These small robots, also known as nanorobots, move through the body and deliver therapeutic ingredients directly to damaged cells, increasing therapy efficacy and reducing side effects. Nanobots present an innovative approach that can handle the disadvantages of traditional methods of dealing with cancer since they transport targeted nanoscale drugs.[8] These nanodevices are able to find their way in the complicated biological environment, react to tumour-specific signals (e.g. pH or temperature), and also facilitate the selective delivery of the therapeutic drug to cancer cells.[9] Nanobots are beneficial because they improve the therapy's effectiveness along with the lower toxicity level through the delivery of the drug to the tumour by controlling the concentration of the drug at the tumour site, which in turn minimizes the off-target effects. Additionally, it is a technique that has great potential for advancing precision medicine technologies such as real-time imaging and controlled drug release.[10] The major technological revolution that presents a new perspective on cancer cure and introduces high-quality medicine that will help in safer and more personal successful management of cancer would be nanobots in cancer therapy.[11]

This review article focuses on the design, mechanisms of action, and therapeutic advantages of nanobots over traditional cancer therapies to investigate the revolutionary potential of these devices in targeted drug delivery and cancer treatment. While emphasizing nanobots' potential as a next-generation precision medicine solution, the article attempts to give a thorough review of recent developments, cutting-edge technology, and difficulties related to their use in oncology.

Conventional cancer treatments

The goal of any treatment against cancer is to kill the greatest number of cancer cells while causing minimal damage to normal tissues. Traditional therapeutic modalities have been the backbone in the management of cancers for decades. Besides the biological ones, cancer is also considered a complex disease from a healthcare and socioeconomic point of view.[12] Poor treatment affordability, side effects, and unequal access to novel medicines worldwide jeopardize patient outcomes. Additionally, drug resistance and a lack of effective treatments for diseases, such as glioblastoma and pancreatic cancer further complicate the need for more innovative solutions.[13] For localized cancers, surgery to remove the tumour is usually the first line of treatment. Even though surgery benefits many solid tumours, in situations where cancer has spread or is located in places where access is impossible, it is limited.[4] Chemotherapy relies on cytotoxic drugs that act against cells dividing fast. Due to its non-specific nature, it has been associated with serious adverse effects such as immunosuppression, nausea, hair loss, despite the fact that it often successfully reduces tumour burden.[14] Conventionally, ionizing radiation has been used during radiotherapy with an intent to damage the DNA of cancerous cells by killing them. The collateral damage to healthy surrounding tissues is outweighed by the actual radiotherapeutic effect in many instances, particularly when sensitive organs like the brain and lungs are targeted.[15]

Recent advances in genomics and molecular biology have opened new avenues to target therapies in such a manner that the drugs could use specific genetic aberrations against tumour cells. Novel treatments involving hormone therapies, small-molecule inhibitors, and monoclonal antibodies act far more precisely upon the signalling pathways of tumour cells compared to conventional techniques of treatment.[16] Examples are the inhibition of the BCR-ABL fusion protein by imatinib in chronic myeloid leukemia,[17] and the inhibition of HER2-positive breast cancers by the monoclonal antibody trastuzumab.[18] Because of the heterogeneity of cancer and further the potential to develop resistances against treatments, even more novel interventions are under study and development. New treatments for cancers under development include nanoparticles, which are a key constituent of nanotechnology, and have been under study for precise medication delivery directly to the tumour sites. Such treatments would deliver higher doses to the tumour site compared to conventional therapies with a significant reduction in systemic toxicity [19, 20].

Development of nanobots for targeted drug delivery in cancer treatment

The manifestation of modern technology in the form of nanorobots, nanoscale robots for targeted delivery of medicine or cancer treatment, is a result of the fusion of nanotechnology and precision therapeutics.[21] The nanoparticles can thus function as the body's transport system to the target site. During cancer treatment, nanobots are presented as very small robots that are swarmed through tumours or the human body and interact with cellular molecules to destroy cells as needed. The technique not only increases the localized concentration of the therapeutic agents and the effectiveness of treatment but also reduces side effects. These are usually made of biocompatible materials, and their propulsion systems enable the nanobots to move in biological environments. [22,23] Various types of solid-state energy storage sources, such as light, magnetic fields, and chemical reactions, are the power sources. [22,24,25,26] As a result of their potential to modulate the TME, novel nanorobots have emerged as the prime candidates for cancer treatments.[27]

The development of stimuli-responsive nanobots, which are able to function under specific conditions, such as changes in pH, temperature, or light, is considered to be among the most important advances in this field.[28] They can, thereby, be targeted and escape the killing of healthy cells. For instance, researchers have made nanobots that recognize and bind themselves to the low pH in cancerous cells, which is often more acidic than that of normal cells. This kind of approach reduces the drug-induced systemic toxicity while improving the drug's efficacy.[29] Concerning the design concept, biocompatible materials such as metals, lipids, and polymers are the main materials that are used to make nanobots. Nanobot designs, which even get a step further, will include sensors and actuators as well as molecular recognition components.[30] Propulsion systems are among the salient elements. Nanobot locomotion is due to a number of systems, of which chemical-powered, magnetic, acoustic, and light-driven are typical examples. Targeting tactics are additional parts of the design. In passive targeting, encapsulation in tumour areas is mainly due to the EPR effect; active targeting is achieved through ligand-receptor interactions. [31,32]

Materials required for the synthesis of nanobots

The fabrication of nanobots involves a multidisciplinary approach: material science enmeshed with engineering and nanotechnology. Material selection will definitely affect the design and functionality of nanobots, which pertains to performance, biocompatibility, and applicability. Thousands of material varieties are used, which are chosen based on the application requirements. Metallic materials include gold and silver as some of the most commonly used metals. The other particle is, in particular, gold nanoparticles, due to their excellent physical, electronic, and optical properties, added to chemical ones. Their good biocompatibility is due to their developers' efficiency and the possibility of their use in such aspects as the fitment of drugs, biosensing, and first and foremost, imaging services.[33] The second most commonly perceived type of nanoparticles, named magnetic nanoparticles, such as iron oxide (Fe_3O_4), has the potential to evolve the magnetic field and therefore to cause effects on the target-specific drug delivery and the possible diagnosis of disease.[34] Some of the materials employed for the synthesis of nanobots include the following:

a) ***Polymeric materials:*** They present another versatile option. Biodegradable polymers such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), are typically selected for the manufacture of nanobot coatings or structures, thereby improving biocompatibility and providing controlled drug release.[35] Stimuli-responsive polymers bring along a creative aspect through their ability to change their properties, such as solubility or shape, in accordance with the changes of the environment, like pH or temperature; thus, they can act as adaptive nanobots.[36]

b) ***Carbon-based materials:*** During nanobot synthesis, carbon-based materials have been recognized as a key component. Graphene constitutes high conductivity combined with a high surface area-to-mass ratio, which is why it is suitable for biosensing. Furthermore, functionalized graphene oxide has shown positive results in active targeting. Carbon nanotubes are also made use of their outstanding mechanical strength and electrical conductance and are capable of easily penetrating the biological membrane, hence applying in drug delivery and intracellular sensing.[37]

c) ***Silicon-based materials**:* Like silicon and silicon oxide nanoparticles, silicon-based materials can maintain their stability and can control their porosity. Therefore, the materials are great, such that they are biosensors, and also, they can be used for controlled drug delivery.[38]

d) Biological material: The production of nano-robots from the biological materials of DNA and RNA is one such task in molecular recognition and drug targeting.[39] The use of proteins and lipids for the development of biohybrid nanorobots due to their natural biocompatibility and functional versatility is already known to be the most common configuration.[40]

e) *Hybrid and other organic materials:* Hybrid materials belonging to a type of materials, such as metal-organic frameworks (MOFs), that are composed of metal ions and organic ligands are the focus. As a result of their large surface areas and the fact that their functionalities can be adjusted based on the target, they are used in specific applications such as drug delivery and diagnosis.[41] Products like titanium dioxide (TiO_2) are in use because they possess photocatalytic features that make nanobots engage with light for water cleaning and medicine applications.[42] The realization of nanobots is only possible if the materials that are carefully chosen to perform some particular functions, including the delivery of a drug, biosensing, or environmental remediation, are introduced. The combination of biocompatible and multifunctional materials is not only necessary for their implementation in real-world applications but also guarantees their success.

Synthesis of nanobots

The synthesis of nanobots integrates nanoscale materials into functional devices capable of performing specific tasks such as drug delivery, sensing, or environmental remediation. This process combines bottom-up nanotechnology, where atoms or molecules assemble into nanostructures, and top-down approaches, which sculpt larger materials into nanoscale features. A detailed understanding of the synthesis methods and techniques is essential for developing these innovative devices. The steps involved in nanobot synthesis include:

a) ***Design and material selection:*** For instance, gold nanoparticles are often selected for drug delivery due to their biocompatibility, while magnetic nanoparticles are preferred for imaging and targeted therapy. Once materials are chosen, various synthesis techniques are employed.

b) ***Synthesis techniques:***

1. ***Bottom-up approaches:*** These methods rely on self-assembly or chemical reactions to build nanostructures from the atomic or molecular level. Techniques such as chemical vapor deposition (CVD) allow gaseous precursors to form thin films or nanostructures like carbon nanotubes and graphene, which are integral to creating conductive components.[43] Colloidal synthesis, another bottom-up method, involves chemical reduction in solution to produce metal nanoparticles like gold or silver, which are vital for imaging and drug delivery applications.[44] Electrochemical deposition is used to deposit metals or metal oxides onto substrates, forming nanoscale patterns crucial for electronic nanobot components.[45] Additionally, biological synthesis employs eco-friendly processes using bacteria, algae, or plant extracts to produce nanobot components.[46]

2. ***Top-down approaches*****:** These techniques, on the other hand, sculpt larger materials into nanoscale structures. Lithography patterns nanostructures onto surfaces using light or electron beams, enabling intricate designs for nanobots used in electronics and medical devices.[47] Mechanical milling grinds larger particles into nanoparticles through high-energy forces, producing materials like oxides for environmental applications.[48]

3. ***Hybrid approaches:*** Combining top-down and bottom-up approaches, such as in microfluidic systems, allows for precise control over self-assembly, resulting in nanobots with specific sizes and shapes.[49]

c) ***Functionalization:*** After the primary synthesis, functionalization and assembly play crucial roles in enhancing nanobot performance. Surface functionalization involves attaching molecules like antibodies, drugs, or targeting agents to nanobots through covalent bonding, electrostatic interactions, or hydrophobic interactions.[50] Actuator and sensor integration introduces components such as piezoelectric materials, magnetic nanoparticles, or nanoscale motors to provide motion and sensory capabilities.[51]

d) ***Assembly techniques*****:** These techniques range from self-assembly, where nanobots form via non-covalent interactions such as van der Waals forces or hydrogen bonding,[52] to pick-and-place robotics, where robotic systems precisely position nanoscale components.[53]

Mechanisms of nanobot action

For upgrading the precision, efficiency, and safety of therapeutic interventions, nanobots are subject to the functioning of a complex set of mechanisms.[54] To bring about the much more exact and efficient administration of drugs compared to the traditional ones, these nanoscale technologies were designed to move in the human body with great precision and target the desired cells, hence, the cancer cells. The nanobots can be used to deliver the necessary drugs to the specific targets in the case of cancer therapy. By transforming the external surfaces of nanobots into selection mechanisms for drug delivery, the sparing of the unwanted impact is one of the basics. These nanobots could be clogged or otherwise functionalized by the covalent attachment of target ligands (e.g., antibodies, peptides, or small chemicals) that are highly specific to the markers or receptors expressed by tumour cells on the surface of the nanobots.[55] For instance, the therapeutic payload is delivered by nanoparticles with anti-cancer antibodies conjugated to the particle, making it attach specifically to the cancer cells. Through the ligand-receptor binding, the mechanism increases the drug concentration in the tumour region while reducing off-target effects, which lessens systemic toxicity.

Another option that nanobots use to release targeted drugs is controlled, triggered drug release. Stimuli-sensitive nanobots are engineered to render their request reaction on a particular place's status.[56] The appearance of such conditions as low pH, hypoxia, or high enzyme activity in the microenvironments of tumours may be a consequence of their application as the releasing agents of therapeutics. In the acidic environment of the contacted solid neoplasm, pH-sensitive nanobots could be selected for shipping. Additionally, thermal triggers can be applied in connection with photothermal therapy when the nanobots contribute to destroying cancer cells by generating heat and delivering drugs.[57]

Applications of nanobots in cancer therapy

Among their most prominent qualities, nanobots are capable of making conventional cancer treatments more precise and flexible, thus making them an integral part of the cancer therapy regimen. These nanoscale devices can cause certain drug compounds to hit cancer cells directly, and, thus, they can help cancer therapy by aiming and minimizing the negative effects of radiation and chemotherapy. The classification of nanobot applications in cancer therapy mainly revolves around the research categories; these are the targeted drug delivery, immunotherapy improvement, gene therapy, and diagnostic. [58,59,60]

a) ***Targeted drug delivery:*** Nanobots are, and have been, used for some years in cancer therapy, in countless ways.[61,62] The targeted distribution of medications is one of the widely observed applications of nanobots. The usual dispersion of drugs inside the body is the non-specific manner, because of which conventional chemotherapy is mostly accompanied by systemic toxicity. Drugs that are curative can be contained in and then are delivered to the tumour areas through the nanobots, thereby, reducing the harmful effects on healthy cells. Treatment results through this delivery approach are the best due to the fact that the tumour sites are super-loaded with the medications.[63] The most recent research has displayed that nanobots have that one exceptional quality of dealing with some disease-causing microorganisms whose stronghold is the brain, like the aggressive forms of cancer such as glioblastomas. To the best of researchers' knowledge, missing the definite mechanism of nanobots loaded with doxorubicin-forced accumulation of tumours through their pH-sensitive means is unproven. [64,65] These tiny machines can also be engineered also to address the peculiar environment of tumours. For example, the low oxygen levels or the high acidity, thus they will deliver their payloads precisely on the targeted areas.[66]

b) ***Immunotherapy enhancement**:* Nanobots also show promise in enhancing cancer immunotherapy. They can improve the effectiveness of treatments aimed at helping the immune system recognize and attack cancer cells by directly delivering immune checkpoint inhibitors, cytokines, or modified T cells to tumours. This approach is especially valuable for cancers that evade immune detection.[67] Nanobots can also transport vaccines or adjuvants to stimulate the immune system, triggering a more robust attack on tumour cells.[68]

c) ***Gene therapy:*** Another exciting application of nanobots is in gene therapy. They can carry DNA or RNA molecules into cancer cells to alter their genetic makeup. This could mean fixing genetic defects, suppressing tumour-promoting genes, or boosting the production of cancer-fighting proteins.[69] Nanobots are particularly useful in overcoming challenges like protecting genetic material from degrading before it reaches its target. By solving these delivery issues, they pave the way for more effective gene-based cancer therapies. The delivery of CRISPR-Cas9 gene-editing tools by nanobots to specifically alter the genomes of cancer cells is one recent development.[70]

d) ***Diagnostic and imaging uses:*** Nanobots are also used as diagnostic agents in the diagnosis of cancer and monitoring of treatment progress.[71] Nanobots are smart enough to enhance magnetic techniques by incorporating particles that can detect fields, X-rays, and fluorescent lights.[72] This in turn, the early tumour detection and the monitoring of therapy efficiency, will be possible through magnetic resonance imaging. They can also incorporate receptors for certain cancer-associated biomarkers, leading to a more accurate and early diagnosis. One way it helps to combat cancer is by its capability of allowing for quick interventions, which is crucial to cancer prognosis improvement. The term "theranostics" denotes the twofold characteristics of nanobots as diagnostic and therapeutic instruments.[73]

e) ***Minimally invasive surgery:*** Nanobots are a non-invasive alternative to traditional methods of surgery. Through the use of precision targeting, they reduce healing time, as well as the need for large incisions, which are done on the cellular level. This is particularly useful for the treatment of tumours in the brain and other inaccessible parts of the body, such as the brain. [74,75]

f) ***Overcoming multidrug resistance:*** Overcoming multidrug resistance (MDR) is yet another way that nanobots are applied in the cancer treatment area. With drug transport to cancer cells or by disturbing the activity of such efflux pumps, which are the primary reason for MDR, nanobots attain the deeper sections of the cancerous process.[76] Multidrug resistance in cancer cells is a vital hindrance to chemotherapy of high efficiency. Efflux pumps, such as P-glycoprotein, which actively throw drugs out of cancer cells, are responsible for the reduced effectiveness of some treatments. Nanobots have been developed to stand against this resistance by carrying the drugs directly to the cancer cells or interfering with the pumps. This method elevates the intracellular drug levels, making the MDR potentially disappear and the curing success become better.[77]

g) ***Synergistic (combination) therapies:*** Nanobots are the basis of a new technology that combines different treatments on one platform. They can substitute immune-modulatory drugs, chemotherapeutic agents e.g., or rather different mixtures that correspond to each separate tumour. The most severe problem of cancer drugs is resistance, which can be confronted with the help of a multifaceted approach.[78] Nanobots can shape the success of therapy and inhibit the appearance of resistant cancer cells by blocking many pathways in which they are involved. Dual-purpose nanobots, which have been found to be responsible for the transport of CRISPR-Cas9 gene editing tools as well as the transport of both gene editing drugs and chemotherapy drugs, have been reported.[7]

Recent advances and research progress

A new advancement has been observed in the use of nanobots for cancer treatment and medication delivery, which has been characterized by some promising developments, such as the utilization of technologies that are at the forefront to enhance therapeutic efficacy, specificity, and safety. Accelerating the delivery of therapeutic drugs directly to tumour cells, nanobots, particularly those having their dimensions in the nanoscale, have the capability to change the cancer treatment process completely by overcoming the drawbacks of conventional chemotherapy and radiation.

a) ***Smart and stimuli-responsive nanobots:*** The use of intelligent, stimuli-responsive nanobots for drug delivery and cancer therapy is one of the most interesting implementations of nanobot technology. In response to particular stimuli such as pH variations, changes in temperature, or the presence of special enzymes or biomolecules, these nanobots can deliver their therapeutic payload.[79] In biomedical applications, including drug delivery, these polymers are crucial for building dynamic, responsive systems that can act and react to environmental cues for a time to achieve the controlled release or other therapeutic actions.[80] In the case of biological conditions, nanobots and nanostructures fabricated by materials sensitive to light, pH, or temperature exhibited dynamic adaptive behaviours. When presented with certain stimuli, these systems consummate reversible modifications like swelling or shrinking, which can be subsequently used to augment the effectiveness of drug delivery, cancer treatment, and other medical procedures.[81]

b) ***Improved targeting and specificity:*** Recent research in the field of nanobot targeting takes into account the narrow-focus drug delivery to the cancer site and off-site effect reduction. Nanobot targeting mechanism development has been the main focus of science lately. AI algorithms and multi-modal imaging such as magnetic resonance imaging (MRI) and ultrasound, not only guarantee the quality of nanobot tracking but also enhance the targeting function. [82,83] For this purpose, the surface of nanobots is given the speed ligands, including peptides or antibodies, which are necessary to link them with the overexpressed receptors or biomarkers on the surfaces of cancer cells. Thus, the aforementioned method of receptor-mediated targeting becomes possible whereby the healthy cells negatively affected through traditional cancer treatments are alleviated. This approach makes use of the unique biological nature of tumours by combining functionalized nanoparticles that are delivered to particular cancer cell markers in the body; thus, the nanotechnology approach will be practical. [84]

c) ***Nanobot-assisted combination therapies:*** The engineering of nanobots that can carry a multitude of therapy drugs at the same time is another significant innovation of the nanoparticle drug delivery systems. For example, researchers are able to overcome medication resistance and treatment failure by incorporating immunotherapy, gene therapy, and chemotherapy into the same nanobot platform.[85] However, for example, nano is biosensing tumour cells and killing them with checkpoint inhibitors or/and chemotherapy drugs. Furthermore, this dual-agent treatment improved tumour detection and inhibited tumour growth *in vivo* and *in vitro* animal models. Moreover, the use of more than one drug in combination therapy reduces resistance or relapse by being effective in a synergistic manner. [77,86]

d) ***Integration of CRISPR-Cas9 and gene therapy:*** Nanobots are increasingly being used in conjunction with cutting-edge gene-editing techniques such as CRISPR-Cas9 for cancer treatment. [7,87] These nanobots have the ability to deliver CRISPR-Cas9 components to tumour cells to suppress oncogenes that promote tumour growth or fix mutations. When combined with nanobots, gene-editing technologies provide a level of precision never before possible in the treatment of genetically based tumours, especially those that have known abnormalities, like *EGFR* in lung cancer or *BRCA1/2* in breast cancer.[88] This strategy may improve the efficacy of conventional therapies like chemotherapy in addition to halting the growth of cancer cells.

e) ***Nanobots in cancer immunotherapy:*** Nanobots have also shown remarkable potential in cancer immunotherapy, which uses the body's immune system to combat cancer. To combat immune evasion mechanisms, immune checkpoint inhibitors or other immunomodulatory drugs can be delivered to the tumour location via nanobots. The immune response is much improved, and systemic adverse effects are reduced when immune therapies can be localized to the tumour microenvironment.[77] To further improve the treatment success, nanobots can also be employed to deliver customized immune cells, including T cells or dendritic cells, that have been altered to target certain cancer antigens.[89]

f) ***Diagnostics and theranostics:*** Nanobots have also shown promise in the field of theranostics,[73] which integrates diagnostic and therapeutic functions into a single platform. It is feasible to treat cancer and track its progress in real time by incorporating imaging agents into nanobots. For instance, nanoparticles can be designed to have magnetic or fluorescent characteristics, which makes it possible to use imaging methods like fluorescence imaging or magnetic resonance imaging to follow the buildup of nanobots at the tumour location without causing any harm. Doctors can improve overall efficacy and patient outcomes by making real-time adjustments to therapy with the use of this ability to track treatment progress.[90]

g) ***Biohybrid nanobots:*** These are yet another advancement in nanobot technology. Natural motility and tumour-homing capabilities are two special benefits of combining synthetic components with organisms like bacteria.[91] Engineered facultative anaerobic bacteria, such as *E. coli*, are designed to thrive in the hypoxic and immunosuppressive environments of tumours. These bacteria produce compounds like L-arginine to enhance immune responses and improve therapeutic outcomes. Additionally, bacterial-nanomaterial hybrids leverage the tumour-targeting ability of bacteria to deliver nanodrugs more effectively, enhancing treatment precision. Specific strains, like attenuated *Listeria monocytogenes*, act as "Trojan Horses," targeting tumour microenvironments by exploiting myeloid-derived suppressor cells (MDSCs) to activate immune responses and clear tumours. [92,93]

h) ***Clinical trials and translational research:*** As nanobots have advanced from preclinical research to clinical applications, an increasing number of clinical trials examining their safety and effectiveness in people have been conducted. [94] A number of nanoparticles have already received approval for the treatment of cancer, including Abraxane (albumin-bound paclitaxel) and Doxil (liposomal doxorubicin). The goal of the upcoming research is to create increasingly sophisticated, adaptable nanobot systems that can provide tailored cancer treatments according to the unique characteristics of each patient. The accuracy and effectiveness of cancer treatment are also being improved by the development of nanobots that can adjust to the changing tumour microenvironment using cutting-edge technologies like artificial intelligence (AI) and machine learning.[95]

Challenges and limitations in the use of nanobots in cancer therapy

Although nanobots have enormous potential for cancer treatment, a number of obstacles and restrictions must be overcome before they can be extensively used in clinical settings. [96,97] These problems cover a wide range of topics, including biological, technical, ethical, and regulatory issues. Here are a few of the main concerns:

a) ***Toxicity and biocompatibility:*** Making sure nanobots are biocompatible is one of the main obstacles to using them for cancer treatment. The ingredients used to build nanobots may still be hazardous to healthy tissues, even though they can be specially made to target cancer cells. The long-term toxicity of some nanomaterials is a problem due to the fact that the materials that are inhaled or ingested are associated with some symptoms that are generally related to inflammation or oxidative stress in organ tissues.[98] For example, the nanoparticles can aggregate at the liver, spleen, and kidneys, damaging them by either causing toxicity or immunological reactions. New strategies to deal with this hazard have been developed. For example, the exposure of reinforced composites and substitution of heavy metals with magnesium.[99]

b) ***Immunogenbots:*** Immunogenbots and its constituent parts have the potential to activate the immune system, which may lead to immunogenicity problems. The immune system is able to make an attack on the nanobots by recognizing them as foreign matter. It is possible that the nanobots would be removed too early from the body, and as such, they are less useful.[100] Besides, the immune system might be activated, thus causing inflammation, which will make the application of nanobots for treating cancer even harder. Surface modification of the nanobot, such as adding polymer chains to the nanoparticles to reduce immunogenicity, is the most common approach; however, it may also be the root of the changes in how nanobots perform and selective targeting.[101]

c) ***Delivery and distribution problems:*** Delivering nanobots that target the tumour location effectively still remains very challenging at the moment. Despite the small size of nanobots, the chance that enough of them will come to the tumour location is not assured. Tumour heterogeneity, or the differences in size, shape, and blood supply of various cancer kinds, is one of the reasons that the competence of nanobots in locating and entering tumours may be affected.[102] Galloping of the nanobots to the tumour zone can also be slowed down by tumour heterogeneity, which is because of the differences in tumour size, shape, and blood supply of the different types of cancer. Besides, in terms of the interaction between the nanobots and the tumour, the endothelial barrier and the tumour’s extracellular matrix can serve as an impediment to the effective diffusion and concentration of the nanobots within the tumour mass.

d) ***Ethical and regulatory issues:*** Another major challenge is the regulatory approval of nanobots. As nanomedicines are at an infant stage, regulatory bodies such as the Food and Drug Agency (FDA) have limited expertise in evaluating their efficacy and safety.[103] Besides thorough preclinical and clinical testing, developing standardized processes for nanobot approval is important and challenging. The use of nanobots in the human body is also still considered a long-term intervention that has ethical concerns, specifically when looking at the potential unforeseen consequences of genetic alteration or nanobot particles migrating to parts of the body that are not intended.[104] Also, there is an involved concern regarding consent, genetic engineering, and nanorobot treatment in relation to immunological-genetic interventions. Apart from stimulating progress, the use of nanobots in cancer treatment also raises some serious ethical and regulatory concerns. The establishment of comprehensive frameworks for assessing the efficacy and safety of these advanced technologies in clinical applications is just one of them. Because nanoparticles and nanobots possess properties that other materials do not, their approval processes often cannot keep pace with the rate of innovation. It is difficult for regulatory bodies to change existing legislation to consider the specific behaviours and risks associated with nanomaterials, such as potential toxicity and environmental concerns. For instance, due to unforeseen issues such as long-term health effects, more detailed research and revised procedures are required to ensure that these technologies meet the necessary safety standards.[105]

e) ***Scalability and cost of production:*** Another limitation is the cost for mass production of nanobots at reasonable prices. The construction of nanobots requires highly controlled materials and processes, which is usually expensive and time-consuming. Moreover, the safety and efficacy of nanobots are highly reliant on production consistency and reproducibility. Although nanofabrication techniques have been developed, there is still some technological and financial barrier for large-scale manufacture.[57]

Future directions

The point of using nanobots in cancer therapy from here on will be to enhance accuracy, effectiveness, and safety during cancer treatment.[106] Development and use of nanobots in cancer will be shaped by a set of emerging critical areas that emerge as nanotechnology research develops further.[107] Some of those potential future directions are integration of sophisticated materials, precision targeting, combination treatments, real-time monitoring, and regulatory developments.

a) ***Integration with new technologies:*** An increasing number of nanobots are designed to act in concert with advanced technologies such as organ-on-a-chip models, machine learning, and AI. AI algorithms can enhance the design and optimization of nanobots by analyzing huge volumes of biological data and hence allow for more precise targeting of mutations unique to tumours and personalized treatment.[108] Additionally, nanobots with organ-on-a-chip models can create realistic preclinical testing settings that can help in forecasting the behaviour of nanobots in human tissues before clinical trials are carried out.[109] These could accelerate research, simplify design processes, and enhance the therapeutic efficacy of nanobots in cancer treatment. A number of recent studies illustrate the potential of novel technologies, including OoC models and nanobots, to improve drug research and preclinical testing. Nanobots designed to work together with OoC models have the capability to act as substitutes for the currently used animal and human tissue and in that way provide more realistic human biology simulations, which will, in turn, improve drug toxicity testing and evaluations of therapeutic efficacy.[109] Since they are much alike to human organs, the fact that most animal models rarely achieve might be the predominant benefit of such advanced artificial models, and that is why they can be very useful for preclinical research and personalized treatment strategies.[110] Afterward, it is expected that the design simulations of such technologies would be greatly revolutionized with the integration of quantum computing. The most precise drug formulations and the prediction of patient-specific reactions are largely based on the timing and accuracy of simulations, which are both aspects that can be dramatically varied by the quantum computing-enabled faster and more accurate analysis of complex biological data. This revolution in preclinical testing and medical research is made possible by the coming together of OoC systems, nanotechnology, and quantum computing.[101]

b) ***Intelligent nanobots and precise targeting:*** Nanobots' capability to distribute drugs or therapeutic agents with a great degree of accuracy is the cornerstone of their potential in cancer treatment.[54] Researchers are researching the development of "smart" nanobots that respond to the specific stimuli at the tumour microenvironment, like temperature, pH, or certain enzymes that cancer cells overexpress. These nanobots would be able to decide and then release medications to the tumour site while sparing the healthy cells through the use of responsive material; thus, this would lessen the harm of conventional chemotherapy. Furthermore, by the development of selective targeting of tumour markers, such as those presented on cancer stem cells or circulating tumour cells, the accuracy of nanobot-based treatments will also be heightened.[106,108]

c) ***Personalized medicine:*** Nanobots also show great promise in precision medicine, particularly in cancer treatment. These nanobots have the capability to combine with proteomic and genetic data in allowing highly personalized treatments. AI is crucial in enhancing the nanobots' capability to precisely target mutations unique to tumours. Recent advances have proven that AI, upon consideration of both genetic and proteomic data, can guide nanobots to target cancer and provide the needed treatment to this date for more powerful cancer treatments.[111]

d) ***Treatment combinations:*** Another promising avenue is the use of nanobots for combination treatments. Nanobots could target cancer cells from several directions simultaneously by co-delivering a number of therapeutic chemicals, including immune checkpoint inhibitors, chemotherapeutic medications, or even genetic material such as siRNA or CRISPR-Cas9 components. The most severe problem of the classic anti-cancer treatments is the immunity of drugs to treatment, against which such a tactic may be the only solution. For instance, nanorobots can be used as carrying tools for fixing the immune system by providing specific medications against tumour cells and doing chemotherapeutical drugs therapies. This alternative that has different components could be the cutting edge of research for those who face this disease again and the most useful medicine in oncology.[97]

e) ***Real-time feedback and monitoring:*** Nanobot advancements in the future will probably incorporate real-time monitoring features. Sensor-equipped nanobots could monitor drug delivery efficacy, changes in the tumour microenvironment, and tumour markers. Clinicians may receive this data, and it could be a very relevant piece of information about how the patient counters the treatment.[112] Moreover, nanobots might be reprogrammed to realize such a behaviour that changes in real-time in response to feedback, thus allowing adaptive therapies that are personalized for the tumour's changing needs. By the use of a real-time feedback loop that ensures that the treatment will always be optimized for, the tumour's changes can lead to the transformation of personalized medicine.[112]

f) ***Immunotherapy mediated by nanobots:*** Immunotherapy has changed the treatment of cancer, and nanobots may make it even better. Immuno-checkpoint inhibitors, cytokines, or modified T cells are the ones that can be sent straight to the tumour site with the help of nanobots. Nanobots, through specific control of the release of those immune-modulating chemicals, might be in a better position to persuade the body to defend itself effectively by doing away with the cancer cells' resistance mechanisms to immune detection.[113] Furthermore, using nanobots with CAR-T (chimeric antigen receptor T-cell) therapy will lead to more targeted and efficient immune responses. Nanobots can be a big advantage in cancer immunotherapy. Their capability of immune checkpoint inhibitors or modified T cell delivery may highly increase anti-tumour immunity. Simplifying the battery of must-have drugs a bit, the current view to utilizing personalized nanoparticles gives prominence to the thought that nanorobots, with the help of specific markers or its specific environment, should be able to release anti-tumour drugs.[113] The pinpoint intrusion of immune-modulating drugs into the tumour microenvironment is what should be realized with nanobots, and it follows that the enhanced immune response and the therapeutic effects will be experienced through this technological advancement.[99,114,115]

g) ***Overcoming drug resistance:*** One of the best ways to control the problem of the resistance of cancer cells to medication can be a nanobot. In the guise of altering the way drugs act in the human body or allowing drugs to be released before they begin to take effect, tumour cells that get used to chemotherapy drugs are born. To bypass these mechanisms, the gene expression of the nanobots can be changed, or they can also be made to co-deliver several drugs. A good example of this would be that along with chemotherapeutic drugs, nanobots can give small interfering RNAs (siRNAs) that silence the genes causing drug resistance and thus increase the efficiency of treatment.[116]

h) ***Advancements in ethics and regulations:*** The ethical and legalistic frameworks in nanotechnology for cancer treatment need to be developed along with the science. In-depth protocols for clinical testing, safety assessments, and monitoring of nanobot-based treatments for a long time to come will be the must-have for future developments. For these treatments to be widely used in clinical settings, regulatory pathways that guarantee their safety, especially with regard to biocompatibility and long-term effects, should be established.[117] In addition, it will be necessary for the public to be willing to solve ethical problems associated with the use of nanobots. These may be either genetic information privacy or consent for new treatments.[104]

CONCLUSION

Nanobots are now used by researchers to treat cancer with a nearly perfect combination of accuracy and potential in targeted medication administration, diagnostics, and minimally invasive therapies. They are truly promising technology for cancer therapy. Nanobots can be used directly to deliver beneficial chemicals to the tumour regions thus, the side effects can be minimized only on the tumour site of the body, and with better treatment outcomes through new mechanisms like stimuli-responsive release systems, surface changes for targeting, and external triggers like light and heat. Not only is there the potential of gene editing and immunotherapy improvement, but novel combination medicines and real-time diagnostics too have so far been introduced as part of the latest research. Safety is predominantly the issue, including aspects like drug resistance, scalability, immunogenicity, biocompatibility, and regulatory approval in the case of nanobots for the clinic. In addition, the progress is likely to be fast with the help of ongoing interdisciplinary cooperation and technical developments such as the integration of artificial intelligence, organ-on-a-chip models, and real-time monitoring. It is a fact that nanobots will play a significant role in the next generation oncology and will be different as new research is coming out, and these issues are resolved.

Conflict of Interest: The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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