IJMPR 2024, 8(6), 109-118

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 6.669

FUTURE PERSPECTIVE: INTEGRATING NANOROBOTS INTO CANCER THERAPY

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Article Received on: 20/04/2024
Article Revised on: 10/05/2024
Article Accepted on: 30/05/2024

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ABSTRACT
Cancer is the second leading cause of death among all the diseases all over world. There are various conventional treatments available in the treatment of cancer such as chemotherapy, radiation therapy, immune therapy and these therapies produce numerous side effects, can produce damage to the normal cells of the body as well as they are time consuming treatments. Looking forward to the targeted treatment approach to treat cancer, application of nanotechnology can prove the better approach than conventional all available treatments. Use of AI tools specifically nanorobot, can deliver the drug to the targeted site without damaging normal cells of the body, can destroy the tumor cells as well as can also diagnose it too. Nanorobot are nanosized devices that carries data storage sites in its structure. Applying correct data in the construction of nanorobot proves beneficial in terms of targeted therapy for cancer. Moreover, biodegradable materials are used to prepare specific nanorobots that can be easily degraded in the human body after destroying the tumor cells or delivering drugs. Among all the numerous applications or nanorobots in the medical field, its application in the treatment of cancer will have impactful success rate.

KEYWORDS: Cancer, Nanotechnology, AI tools, Nanorobot, Tumor cells.

INTRODUCTION
Globally cancer is the predominant health issue and second reason of mortality among people worldwide next to the cardiovascular diseases specifically in U.S. however in U.K it causes highest mortality among humans.[1,2] Approximately 1300 people die because of cancer on daily basis as per the reports of national Cancer Registry Programme of the India Council of Medical Research (ICMR). In a short time period, there are 19.3 million cases diagnosed with cancer, and as per the reports of 2020 around 10 million deaths by this disease. GLOBOCAN 2020 estimated 19.3 million incidences and 10 million deaths due to cancer worldwide. From the 100% ratio the highest numbers of (2.26 million, 11.7%) cases were denoted for female breast, lungs has the moderate numbers (2.21 million, 11.4%) and the least numbers (1.41 million, 7.3%) are denoted for prostate cancer. The death rate shows the vital reasons for cancer death were lung (1.79 million, 18%), liver (830,000, 8.3%), stomach (769,000. 7.7%) and breast cancer (680,000, 6.9%) of total numbers.[3,12]

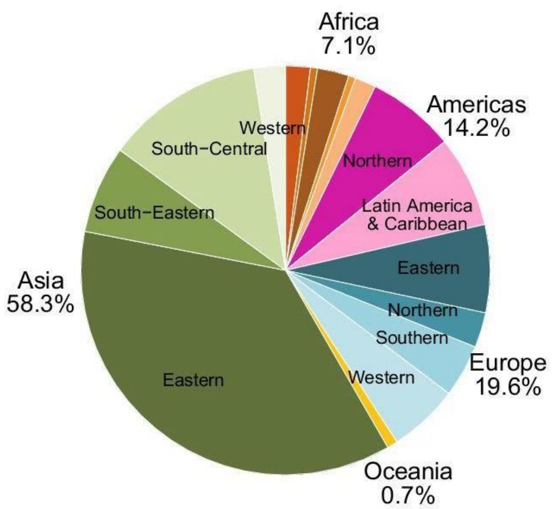


Fig. 1(a): Cancer Incidence rate.[3]

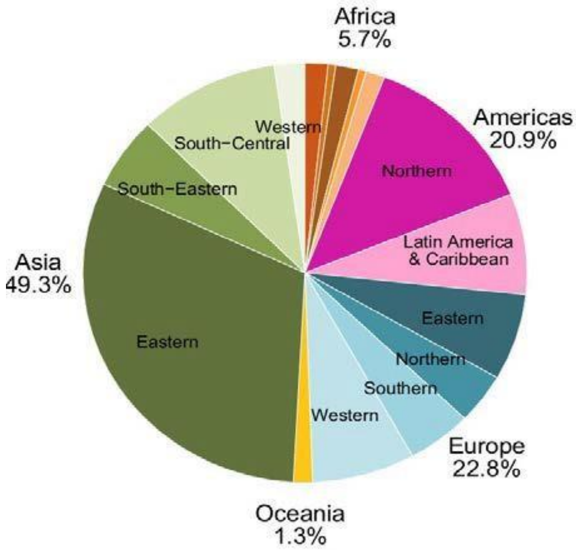


Fig. 1(b): Cancer Mortality rate.[3]

The cancer is divided into four stages which is described by the system known as TNM system. TNM stands for Tumor- refers to the size of tumor, Nodes- it has spread to the lymph nodes and Metastasis- means the cancer has spread to the other organs. The treatment varies from stages as chemotherapy, radiation therapy, or a combination of both surgery, immunotherapy, targeted cell therapy, stem cell therapy, and hormone therapy which are presently in use. Cancer can be cured if its diagnosis is done at earlier stage. Among all available treatments, chemotherapy and radiotherapy are majorly used (about 60%) to treat cancer. But both of the treatments have a common downfall that the person's body cannot tolerate the high concentration of drugs. There are some boundaries for anticancer medications that leads to result as cytotoxicity of normal stem cells which proliferate quickly, such as bone marrow, macrophages, gastrointestinal tract, hair follicles, which leads to effect like myelosuppression, mucositis, alopecia, organ malfunction, thrombocytopenia and hematological side effects among other things. The conservative chemotherapeutic drugs have some drawback that it is incapable to target malignant cells exclusively. This may result in delay treatment, reduce drug dose or intermittent stopping of the therapy. However, in case of cancer immunotherapy, if the drugs are delivered though nanomedicines, they should overcome any hindrance for nanoparticle delivery. However, there are high chances that these nanoparticles could be mistaken as unwanted foreign bodies by our immune system.

Nanorobots travel as blood-borne devices which can aid some crucial procedure of therapy such as early diagnosis and smart medication administration. A smart chemotherapy for administration of medication to give an efficient early dissolution of cancer through targeting only the neoplastic specific cells and tissues and preventing the surrounding healthy cells from the toxicity of the chemotherapy drugs are being used. Nanorobots are also used as drug transporter for timely administration of dose which allow chemical compounds to kept in bloodstream for as long as needed, giving these characteristics for chemotherapy in the therapies for anti-cancer.[4]

Nanorobotics[5]

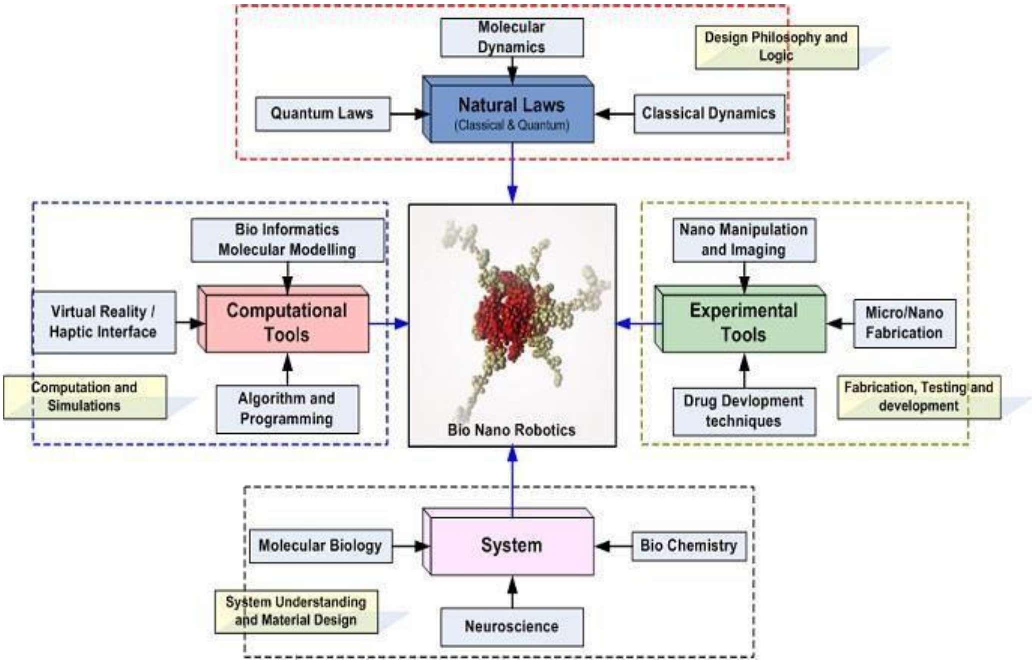


Fig. 2: Nanorobotics: A Multidisciplinary Field.

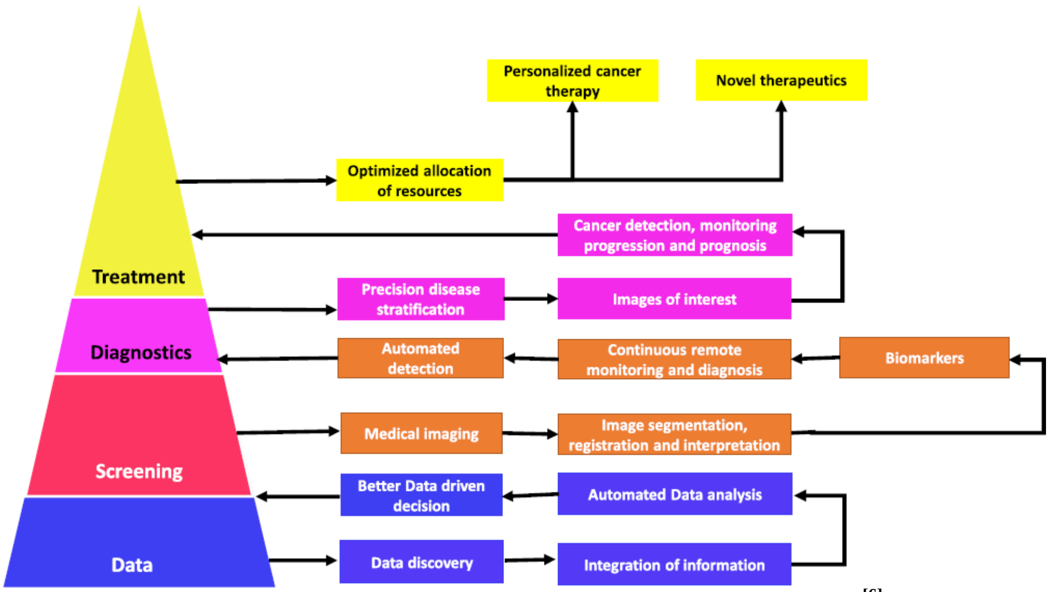


Fig. 3: Artificial intelligence (AI) in cancer medical diagnosis.[6]

Recent breakthroughs in the field of medicine have leveraged nanotechnology, with promising results. The integration of AI tools with nanotechnology has enabled a deeper understanding of the intricate processes within nano systems, thereby facilitating the design and development of pharmaceuticals within these systems. Nanomedicine has witnessed significant growth and ongoing advancements, leading to successful experimentation with various approaches to deliver curative treatments in precise doses.[8] Instant disease prevention can be also enabled by the nanometer-scale device which are able to redefine healthcare, conducting surgery within the body and transforming treatments. A ground breaking shift, with AI-powered nanorobots operating at the molecular level, reshaping healthcare and material science can be remarked by a division of AI and nanotechnology. The technology and design of 1-100nm scale are used. To form the expanding field of nanotechnology combinations of physical, chemical and biological areas of science like medicine, chemistry, physics, material science and biology are required. This field includes science and technology for diagnosing, treating and preventing illness, traumatic injury, and alleviating pain, conserving and enhancing human health using nanoscale architecture materials, biotechnology, and genetic engineering, eventually new building blocks of engineering that can form complex machine systems and nanorobots which are also known as "nanomedicine".[4]

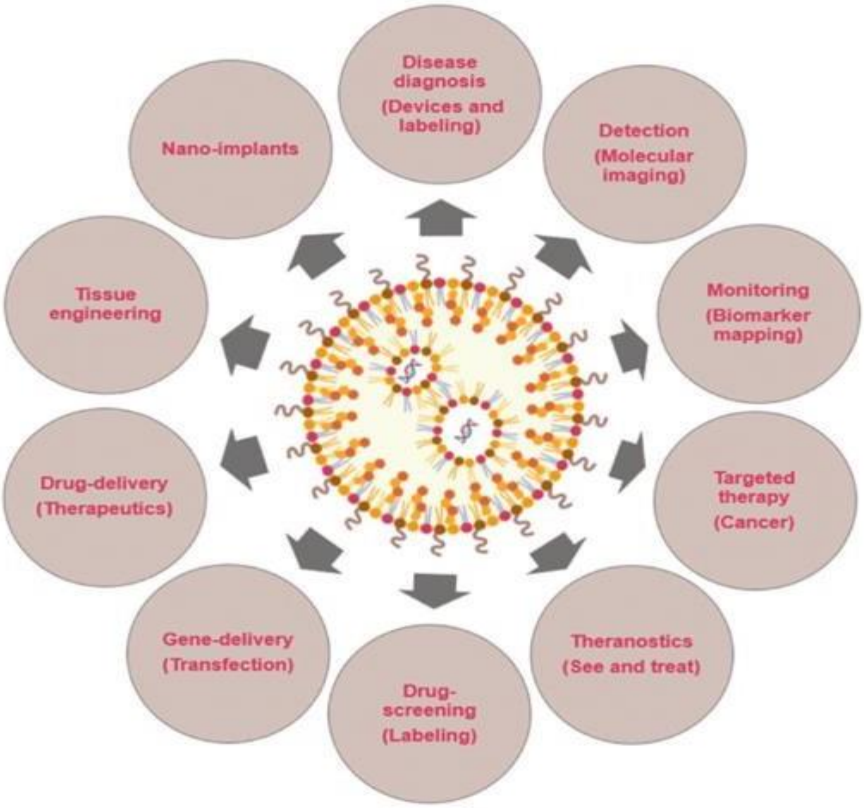
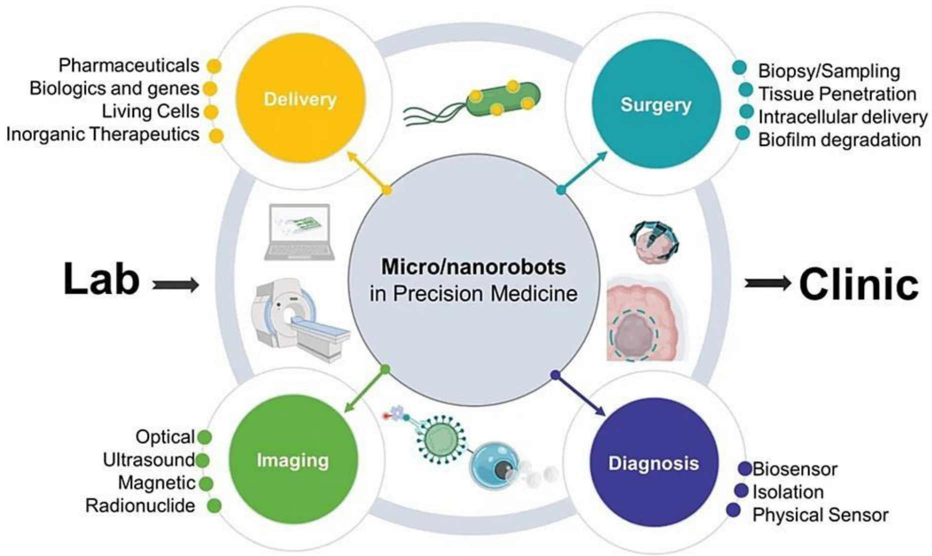


Fig. 4: Applications of nanotechnology in medicinal field.[4]

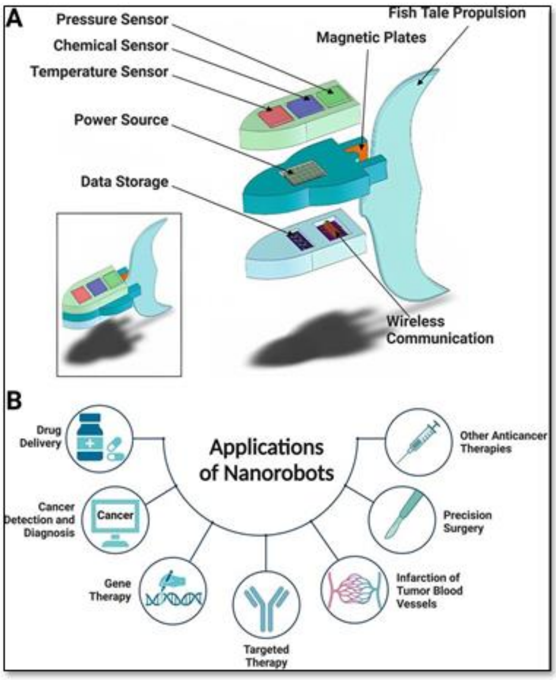


Current trends of micro/nanorobotics in precision medicine[4]

Nanorobots can be used in the fields like medicine, manufacturing every production and environmental cleanup. New scientific discoveries and deeper understanding of the nanoscale world can be induced by the nanorobotics.

Nanorobot[8]

An artificial robot which can freely diffuse in the human body and can interact at the molecular level with specific cell is define as a "Nanorobot". The size of robot varies from 1 to 100 nanometer which is 10 time smaller than a normal blood cell are known as miniature robots.[8] They are emerging technology of this century where up to 1 nanometer of machine parts are being manufactured. These are machines with nanoscale intelligence and contain information that can sense signal, respond and process. In collaboration with medicine, these nano-devices developed to perform specific tasks with precision at the nanoscale and are programmed as an emerging technology. In medical fields, nanorobots are designed to perform specific tasks at cellular levels.[8,9] The nanobots enter the body through direct injection into the bloodstream and then act as an internal surveillance system for the human body. They can sense changes in environmental stimuli, detect for a molecular assembly and diagnose different health conditions. In combination with next-generation software platforms, they can be utilized as a strong diagnostic and monitoring tool. Nanobots can be utilized by healthcare service providers to monitor a patient's health, assess their daily dietary needs as well as administer medicines. Two categories of nanorobots are most widely used in researches- (A) organic and (B) inorganic. Organic nanorobots are called as bio-nanorobots which contain molecular machines and work on ATP and DNA based mechanisms. These nanorobots are less toxic and does not develop any immunogenic response. Inorganic nanorobots are also called as chemical- nanorobots that are developed from carbon particles (diamond structures), synthesized proteins and various types of materials.[9] As a consequence of their small sizes, nanorobots can directly interact with cells, penetrate into them and provide direct access to the cellular machineries. They are capable to deliver payloads (drugs, genes, sensing molecules, etc.), perform certain biomedical functions such as diagnosis and therapeutic actions, have targeting ability to finding out tumor/disease sites, as well have an active or passive power systems which are capable to receive external power sources for example NIR light, ultrasound, magnetic driving force, etc or to to use the mediums/blood flow existing in a biological system.[10]



Structure & applications of Nanorobot[10]

Construction of nanobots

These are very tiny robots having size of only 35 nm in diameter and 200 times smaller than RBCs[1] There are three main points should be considered to design the robots and they are navigation, power and how can the bots can move in blood vessels to reach their target site. Nanorobots can be directed to the cancerous cells through ultrasonic sensors that are emitted by the nanorobot. Nanorobots can also be equipped with a small miniature camera as the nanorobot is not designed to float passively through the bloodstream and it will need some kind of propulsion force to move around the body. As it has to move against the blood flow, the propulsion system has to be comparatively stronger according to its size. If patient's safety is considered, the system must capable enough to move the nanorobot without causing any harmful effect to the host.[8] The structure of the nanorobots can be designed by the researchers by using an open-source software, named as Cadnano. DNA origami is used to build these robots. These bots have an appearance like a nano-sized open-ended barrel that contains two halves that can be opened and closed in the form of a clamshell and these two halves are interconnected through molecular hinges. They kept together by molecular locks or latches which comprise DNA double helixes. There are 12 sites for attaching payload molecules inside these robots. However, on the outer side, two positions are there to which aptamers can be attached (short nucleotide strands with special sequences for recognizing molecules on the target cell). The drug is loaded inside the nanobot, and it is secured by molecular anchors.[1] Nanorobots can be coated by various agents depend on their application or tissue destination. The critical point is external shell as it is acknowledged as a part of the body (internal coating) and capable to release distinguish ideal matrix which it is not toxic at the nanometer level. The pore size can be tuned permitting release of different size molecules (tunable porosity). A firm shell-like silica is present as a molecule. Simple chemical methods can be used to make the smoothly functionalizable however, the most important thin is the silica is not biodegradable and by this it permits a long-term activity of nanorobots in the body.[8]

Materials of nanorobot

Nanorobots are made of biocompatible or biodegradable materials in most of cases. These biodegradable materials dissolve or disappear at the end of performing their tasks. Simultaneously, they should be able to fulfil numerous tasks that are precise and consists of sensing of the presence of tumor cells/tissues, delivery and release of nanocargoes upon stimulations upon physical cues, certain disease biomarkers, changes of local temperatures/pH values and many more. These materials should be flexible and deformable to give surety to give their workability and mechanical properties of nanorobots to work in the human biological microenvironments. They need to be more maneuverable in three dimensions, in viscous and elastic body fluids, as well as in phantom organs.[11]

Nanorobots core

In the core project of nanorobotics, DNA origami is one of the greatest developments. A single- stranded DNA can be collapsed into a two-dimensional shape after that it is converted to a three-dimensional nanostructure, that can release its payloads after binding with a specific cancer biomarker. Viral capsids are robust and able to form nanoparticles are stable in the surrounding environment. This is an innovative design of nanorobot for its use in natural systems. Moreover, to that the protein-rich shell of viral capsids protects viral nucleic acids against denaturation produced by the external environment. The receptor that become the part of the surface of the virus envelope to enable the initiation of conformational changes in the envelope structure and the release of nucleic acid into the selected host cell. It is conjugated with a biomarker or molecule corelated to the receptor nanoparticles that are inspired through the chemical modification of natural polymers. Natural polysaccharides are the most logical choice when there is movement of biocompatibility to the top of the list. Among all, chitosan has been broadly used to form nanoparticles in the last decade. In addition to chitosan-derived nanoparticles, different nanoparticles such as gelatin, alginate, pectin, chondroitin, and dextran have been extensively used in cancer therapy.[11]

Fabrication of nanorobots

Small-scale robots can be formed through the need of active materials which transfer various forms of energy to the motion continuously. Initially, formation of nano-engines for small- scale robots depends on their simple geometry as well as manufacturing procedures. Fabrication of early nanorobots are done by electrochemical reduction of salts and their correlation with the metals within nano/micron symmetric pores. However, another approach can be self-assembly of nanocomponents like layer-by-layer assembly of sequentially charged materials, the generation of self-organizing polymers to form bowl-shaped stomatal cells that can be filled with catalytic materials in their internal spaces and the attachment of colloids to create engineered structures and magnetic links. Fabrication of nanorobots can be done by use of a thin film layer on a template for the production of an asymmetrical coating formation. From polymers to metal beads, different strategies for the formation of nanorobots make use of different commercially accessible micro templates and biological and bioinspired templates. To design and fabrication of more complex nanorobots, 3D printing, glancing angle deposition, rolled-up lithography and other modern techniques are used. Each of these new researches provides novel capabilities to design high quality nanorobots, yet they are more expensive and have limited availability for materials. Biohybrid nanorobots were fabricated with diverse methods as well as they use living organisms and synthetic components, which were coupled together by electrostatic interactions-driven self-assembly.[11]

Components of nanorobot

The main component of nanorobots is surface unit carbon, because of its inertia, adaptable resistance, diamond or C type. The other components hydrogen, oxygen, nitrogen, sulphur, silicon and fluorine for the nanoscale.

Nanobot Room

A) Medicine Chamber

This is a hollow portion inside the Nanobot which contains small doses of medicine. This medicine is delivered by nanorobot is able directly to the site of injury or infection even it can also deliver the drugs that are used in the treatment of cancer chemotherapy.

B) Probes, cutters and chisels

These probes, cutters and chisels are used to remove plaque and clogs. They help nanobots to grasp and break down matter. There is also inclusion of some additional tools to crush the clumps into tiny objects.

C) Microwave Transmitter and Ultrasonic Signal Generator

Cancer is spread by ruptured cancer cells which release certain types of chemicals. If microwave or supersonic signals are turned on by precisely they support nanorobots to break chemical bonds inside cancer cells and destroy cancer cells without damaging cellular membranes.

D) Electrodes

Nanobots use electrodes to generate an electric current that heats the cells until they are destroyed.

E) Laser

Harmful substances like cancer cells, blood clots and plaques can be burnt by the power laser. These lasers vaporize the tissues by producing heat. Vaporizing cancer cells is a difficult task using a powerful laser that does not damage surrounding tissue.

F) Power supply for nanobots

Power is accessible for both outdoor and indoor nanobots. Harvesting energy is directly coming from the bloodstream where the nanorobots utilize the patient's body heat to produce electricity like a navigation system.[11]

Working of Nanorobots

Considering the working mechanism of nanorobts, they are programmed to work by operating them in 2 states - ON and OFF. The drug is delivered by the nanorobot once they recognize a target cell depending upon the presence of surface proteins. The two halves of nanorobot open up and the drug is delivered to that particular cell (on position). In the off position, they are closed firmly and bypass healthy cells. The nanobots are controlled by an aptamer-encoded logic gate. Any type of nanoparticle can be transformed into autonomous biocomputing structures that are capable of executing Boolean logic gates (NAND, NOT, AND, and OR). Since DNA is a natural substrate for computing, it has benefitted a diverse set of logic circuits and robotics. The logic-gating functionality is incorporated into the DNA, and the logic gating is achieved through input-induced disassembly of the structures in the DNA. Different forms of DNA-based biocomputing have already been demonstrated.[10]

Degradation of nanorobots

Nanorobots are formulated and operated in various ways, however, toxin-free degradation is of remarkable importance for biosafety. The degeneracy of materials present in nanorobots is an important factor to be considered primarily before their biomedical applications. High degradability could avoid the post-use operation of the nanorobots.[10]

Pros & Cons of Nanorobot[1,8]

Pros

- The speed and longevity
- Minimization of errors produced by surgeon
- Best targeted drug treatment as well as controlled release of drug
- Used as the replacement of current therapy for cancer and by this side effects can be prevented
- There will be deep understanding of the complexity of human body and brain with the help of nanorobots. This development will further support the performance of painless and noninvasive surgeries.
- The nanobots are tiny in size and they are not visible with naked eyes which provides ease of their administration in a human body by injectable route
- Their bioavailability is enhanced through nanorobotic drug delivery systems
- The errors are minimized because of IT control and automation
- If the drug molecules carried by the nanorobots are square and free to move where needed, the advantage of huge surface space can be realized throughout the mass transfer process.
- Computer control knobs are present to adjust volume, frequency and release time
- The drug is inactive in areas that do not have any requirement of treatment, which minimizes unwanted side effects.

Cons

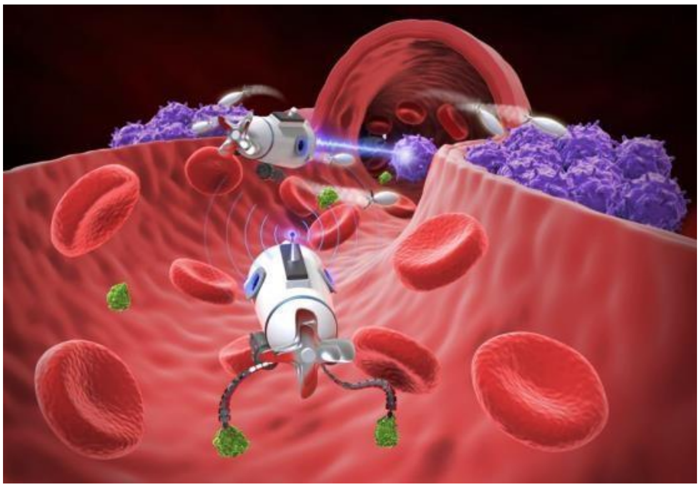
- High cost as well as many complications are associate with its designing.
- If nanobots are misused by terrorists, they could even be misused as bio-weapons and may become a threat to the society.
- If nanobacteria are present in our body they can cause detrimental side effects in our body, so can nanobots which are foreign to us.

- If nanobots self-replicate, a dangerous version of the bots could be produced.
- Electrical systems may develop stray fields that can activate bioelectrically based molecular recognition systems in biology
- Electric nanorobots are vulnerable to electrical interference from external sources such as RF or electric fields, electromagnetic pulses, and stray fields from other *in vivo* electrical devices
- Difficult and complex to connect, adapt and design
- Nanorobots could pose a brutal risk in the field of terrorism.

Applications of Nanorobot[11]

1) Utilizing nanorobots to address blood clots
2) Implementing nanorobots for the diagnosis and treatment of diabetes
3) Incorporating nanobots in the management of kidney stones
4) Leveraging nanorobots for cancer treatment
5) Exploring the use of nanorobots in addressing arteriosclerosis
6) Researching nanorobots for nerve regeneration
7) Developing nanorobots to aid in the elimination of parasites
8) Applying nanorobots in the healing of skin diseases
9) Analysing the surface antigens of each cell type to determine its health status.

Application of nanorobot in the treatment of Cancer[4]



Now-a-days the applications of nanotechnology have come under great focus in the health care field. Clinical therapies are time consuming as well as costly in terms of usage of different medicines to treat the diseases. These therapies can be shifted cheaper, faster and better treatments methods with the use of nanotechnology. Moreover, specific tissues can be targeted using drugs to a accurately located cells and tissues that make the drug more efficacious and reduce side-effects. Under this nanotechnological developments, nanorobotics is an emerging technological field that create machines and robots for infinitesimal things at molecular level.[14]

Focusing on cancer diagnosis and treatment, the development of nanorobots could bring impactful advances with the use of nanorobotic drug delivery systems including surgical and cellular repair nanorobots. The nanorobots are currently designed to recognize 12 different types of cancer cells. Besides this, the molecular motors added in this equipment can change their response to UV light and passthrough cellular layers to produce necrosis and medications to target specific areas. Nanoparticles also (NPs) are also significant role to develop novel methods for cancer diagnosis. Various useful NPs are cantilevers, nanopores, nanotubes, and quantum dots.[9,11]

The major objectives for development of nanorobots in the cancer treatment are

- Monitoring of the patient's body consistently and it is capable diagnose diseases including cancer at initial stages.
- To damage cancerous cells without its effect on other normal cells.
- Reduction of recovery time for the patients of different diseases as well as cancer patients.
- Numerous anticancer drugs can be delivered into the tumour cells with the help of nanorobot without disruption of healthy cells of the body. Moreover, they also reduce side effects of traditional chemotherapy for the cancer.
- Tissues can be repaired, blood vessels can be cleaned, physiological capabilities of airways can be maintained as well as aging process can be counteracted with the help of nanorobot.

Nanorobots have the incredible ability to detect tumor cells by targeting a protein and polymer called transferrin, which effectively obstructs the natural iron uptake of the cancerous cells, ultimately leading to their demise. These nanorobots eliminate cancer cells without causing harm to healthy cells or inducing any adverse side effects.[5] They can revolutionize chemotherapy by precisely administering medication and promoting early cancer dissolution, specifically targeting neoplastic cells and tissues while shielding surrounding healthy cells from the toxicity of chemotherapy drugs. Nanorobots also serve as efficient drug transporters, ensuring timely and sustained release of chemical compounds in the bloodstream to achieve optimal pharmacokinetic properties for anti-cancer therapies. Clinical applications of nanorobots encompass diagnostic, therapeutic, and surgical purposes, typically administered through intravenous injection. By enhancing chemotherapy pharmacokinetics and allowing the body to recover prior to subsequent sessions, nanorobots have the potential to significantly advance cancer treatment.

Nanorobot‑assisted cancer diagnosis and targeted therapies

In the realm of cancer treatment, a new targeted therapy has emerged, offering a more precise approach by interacting with specific biomarkers associated with tumor development and impeding tumor growth. Recent advancements have seen the development of antitumor therapies utilizing nanorobots, which hold the potential to deliver targeted therapy while minimizing the adverse side effects commonly associated with traditional chemotherapy. These power-driven nanorobots can accurately target lesions, execute controlled movement, detect, position, and deliver therapeutic compounds in a precise manner. Additionally, there are tumor-detecting nanorobots capable of examining tumor cell growth *in vivo* using positron emission topography. To ensure safety, an embedded system allows for the pre-programmed control of nanorobots on the Arduino software platform, which are fabricated using isotope-labeled nano-carbon material to mitigate potential side effects on the human body. With their reliable stability and safety, these nanorobots do not pose harm to the human body following injection.

Directions and criteria for nanorobots in clinical cancer treatments

The development of new tumour-detecting or killing nanorobotic tools is a crucial focus in cancer treatment research. Future clinical trials involving cancer patients will provide valuable evidence regarding the effectiveness of nanorobots in anti-tumor therapies. However, current studies on these nanorobots are still in their early stages, and there is a long road ahead before they can be integrated into clinical practices. Substantial efforts are required to transition nanorobots from animal model experiments to applications in living human organisms. Several factors, such as the development of safer materials with improved biocompatibility and degradability, higher power conversion efficiency, and other foundational advancements, are crucial for the progress of nanorobots in clinical surgery. For medical nanorobots intended for cancer treatment to gain widespread acceptance in clinical practices, they must meet specific key criteria. These prerequisites are fundamental requirements that any medical nanorobot must satisfy[10]

1. The safety of medical nanorobots is crucial for their successful integration into clinical practices. Rigorous preclinical and clinical testing is necessary to assess their safety, biocompatibility, and potential side effects. Robust quality control measures during the manufacturing process are essential to minimize malfunctions and ensure consistent performance. Additionally, nanorobots should be designed to be biodegradable or easily removable from the body after completing their therapeutic purpose to prevent long-term accumulation and potential toxicity.
2. Future nanorobots should mimic the natural intelligence of biological counterparts, allowing for precise control, high mobility, deformable structures, adaptive and sustainable operations, and complex functionality. This biological mimicry will enable better adaptation to the human body and enhanced treatment efficacy.
3. Advancing the swarm intelligence of nanorobots toward group motion planning, machine learning, and AI toolbox at the nanoscale is crucial for enhancing their capabilities in precision treatments. Coordinated actions and increased adaptability in complex biological environments can be achieved through this advancement.
4. Nanorobots of the future should be capable of integrating with modern bioimaging and feedback control systems for precise targeting and monitoring of treatment progress. This will enable arbitrary four-dimensional navigation of many nanorobot systems within a living body, ensuring accurate treatment delivery.
5. Innovative nanotechnologies are needed to propel nanorobots to the next level and enable cooperation with the latest advances in cancer medicine. For instance, attaching different types of biomolecules to nanorobots as guides can target specific cells, such as immune cells, to stimulate immune responses, potentially advancing cancer immunotherapy and improving treatment outcomes.
6. Considering financial feasibility is crucial for achieving the transition from the lab to the clinic. The financial costs must be carefully evaluated to ensure successful implementation.

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