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ADVANCES OF MEDICAL NANOROBOTS FOR FUTURE CANCER TREATMENT.

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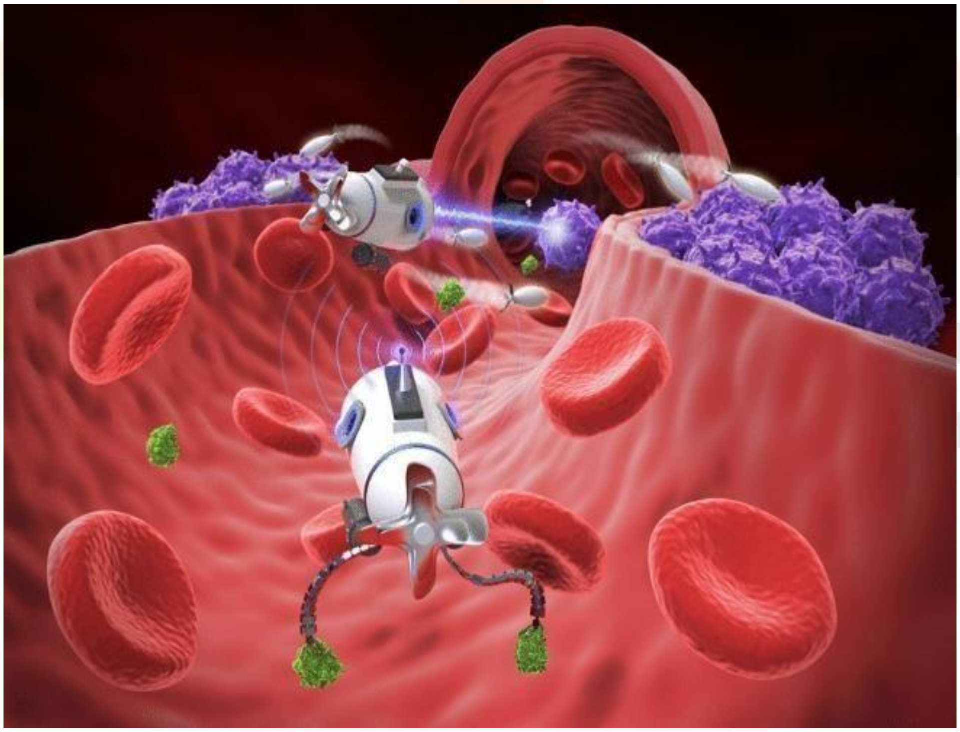
ABSTRACT:

Medical progress depends on the creation of new, more effective cancer treatments. Nanobots represent a promising use for nanomedicines and are currently leading the way in transdisciplinary research. Advances in nanotechnology have made it possible for nanobots to assemble. The application of functional molecular/nanoscale devices, which are being used more often in cancer therapy and diagnosis. Drug delivery, tumor sensing and detection, targeted therapy, minimally invasive surgery, and other complete treatments are among the recent advances in nanobots for cancer treatment. This study examines and evaluates the most recent developments in the field of cancer therapies employing nanobots, emphasizing their essential characteristics and uses in drug administration, tumor detection and diagnosis, targeted therapy, minimally invasive surgery, and other extensive medical procedures. It is anticipated that in the future, medical nanobots will develop in sophistication and ability to carry out a variety of medical tasks.



KEYWORDS: Nanorobots, cancer treatment, Drug delivery, Targeted therapy.

INTRODUCTION:

Nanomedicines were created with the goal of treating, preventing and enhancing human health.
[1,2] the past several decades[3,4] the field of nanomedicines has developed incredibly quickly. Permit one to carry out a variety of medical tasks and gain access to hard-to-reach bodily parts.[5,6].

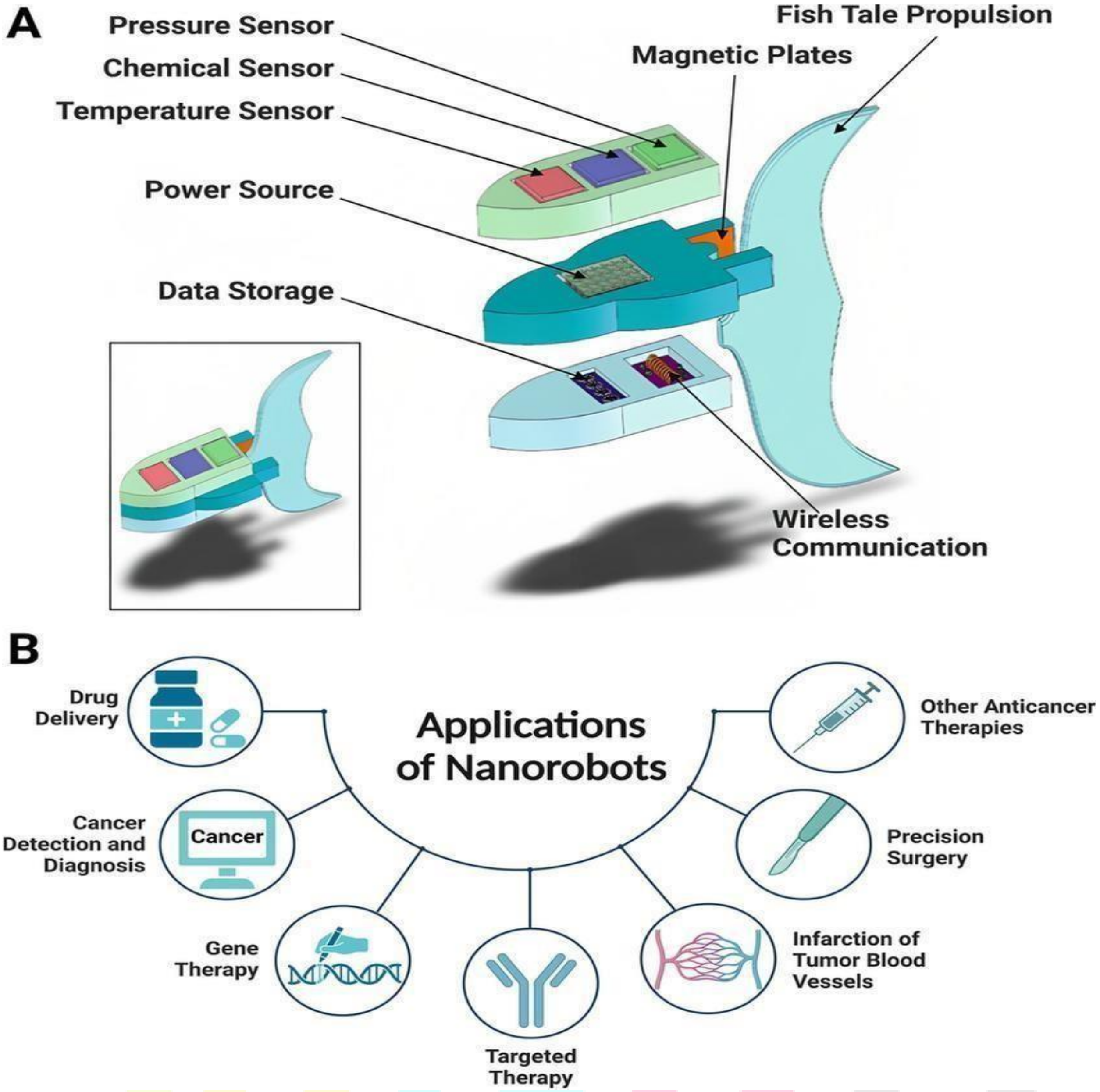


Fig.1

Core structure of nanorobots with their components and applications. A view of a fully functional, autonomous nanorobot for cancer treatment and individualized components.

Health care untethered nanostructures with an engine or the ability to convert various energy sources into mechanical forces and carry out medical tasks are referred to as nanorobots.[7,8]Nanorobots, which are nanoscale devices that can carry medications, genes, and sensing molecules, are extensively employed in the diagnosis and treatment of cancer. Attain a specific biological purpose, possess the capacity to target tumor and illness locations, and possess an active or passive power system that can take in electricity from outside sources.[9]Nanomedicine can be seen as an integral component of nanorobots, independent of an active power supply. Development of cancer-killing nanorobots in an effort to modernize medicine and incorporate them into clinical settings. The implementation of these nanorobotic instruments in actual clinical settings is one of the unfulfilled and significant difficulties of nanorobotic technology.

Composition of Nanorobots:

- **Biochip:**

Photolithography, novel biomaterials, and nano electronics are all used in tandem during the synthesis process. It can be utilized to produce nanorobots for common medical uses, including medication delivery, diagnosis, and surgical instruments. Biochips are currently used in the electronic sectors for manufacturing. Biochip-equipped nanorobots can be included into nanoelectronics devices to enable teleoperation and enhance medical instrumentation capabilities.

- **Bacteria Based:**

This method makes use of biological microbes, such as the bacteria Escherichia coli. The model’s means of propulsion is a flagellum. This type of biological integrated device is typically controlled through the use of electromagnetic fields.

- **Positional Nano Assembly:**

In 2000, Robert Freitas and Ralph Merkle began drafting a research agenda with the express goal of creating a positionally controlled diamond mechanic synthesis and a diamonded nano factory, which would enable the creation of medical nanorobots with diamond coatings.

- **Nubots:** is an abbreviation for “nucleic acid robots.” Nubots are synthetic robotics device.[10]

Natural nanorobots existing in biological systems:

Have seen significant advancements in nanotechnology over the last few decades, with many new nanotechnologies being discovered and used in a variety of industries. However, some amazing naturally occurring nanomachines that might be thought of as "bionanorobots" [11,12]are provided by living things, numerous biological processes depend on these naturally occurring nanorobots, which are capable of both rotating and transporting chemical cargoes along predefined paths with sub nanometer accuracy and excellent efficiency. Energy is used by a variety of naturally occurring biological nanorobots to carry out their designated tasks and convert it into mechanical labor in living systems.

We can now better comprehend the distinctions and similarities between these nanometer systems because to recent developments in the methods used to study the processes and molecular structure. Numerous naturally occurring biological nanorobots function in living systems and may have potential use in medicine. Many scientists have recently conducted research on artificial Nano machineries, inspired by natural nanorobots, to mimic these bionanorobots and address the issue of cancer treatment at the nanoscopic level. [13]

Mechanism of Nanorobots:

One potential avenue for providing physicians with novel medical devices is the research and development of nanobots, which are robots with embedded nano biosensors and actuators. In order to properly promote new medical technologies, controls are looked after. The 1980s saw the development of microelectronics, which resulted in the creation of novel instruments for biomedical instrumentation and the miniaturization of medical systems toward integrated health care, allowing for the efficient construction of pathological prognostic techniques. Clinical procedures have greatly improved in recent years due to the reality of using tiny gadgets in surgery and medicinal therapies. Catheterization has proven to be an effective technique for both cardiac and brain surgery. We are currently making progress toward the miniaturization of devices from micro to nano electronics thanks to the development of biomolecular research and novel production techniques.

Medical Applications of Nanorobots:

Robots are predicted to make it possible for patients with various illnesses to receive new therapies, which will signal a significant advancement in medical history. Among the nanomaterial's being researched for use in nanomedicine include dendrimers, liposomes, and nanoparticles. Nanoparticles can now be used to deliver medications to certain cells thanks to advancements in nanotechnology.

A similar strategy might be used to enable nano robots to distribute anti-HIV drugs. Nano robots will be used in chemotherapy to fight cancer by precise chemical dosage administration. As auxiliary devices for wounded organs, nanorobots could be utilized to process particular chemical reactions in the human body. One potential use for nano robots is to monitor diabetes and regulate patients' blood sugar levels.

Nanorobots in Cancer Detection and Treatment:

Cancer can be successfully treated with current stages of medical technologies and therapy tools.
However, a decisive factor to determine the chances for a patient with cancer to survives: how
Earlier it was diagnosed; what means, if possible, a cancer should be detected at least before the
Metastasis has begun. Another important aspect to achieve a successful treatment for patients is The development of efficient targeted drug delivery to decrease the side effects from chemotherapy. Considering the properties of Nano robots to navigate as blood Borne devices, they can help on such extremely important aspects of cancer therapy. Nano robots with embedded chemical biosensors can be used to perform detection of tumors cells in early Stages of development inside the patient's body. Integrated Nano sensors can be utilized for such A task in order to find intensity of E-cadherin [62-64] signals. Therefore, a hardware architecture .
Based on Nano bioelectronics is described for the application of Nano robots for cancer therapy.
Analyses and conclusions for the proposed model are obtained through real time 3D simulation.

Nanorobots in Gene Therapy

Health care By comparing the molecular structures of the DNA and proteins found in a cell to desired or known reference structures, nano robots can easily correct genetic disorders. After that, any anomalies can be fixed or the needed changes can be made directly in the editor. Chromosome replacement therapy may be more effective in certain cases than repair. Some genetic upkeep is carried out by an assembler-built repair vessel that floats inside the human cell's nucleus. The Nano machine gently stretched a supercoil of DNA between its lower pair of robot arm

opens a path for the unraveled strand to be examined further. In the meantime, regulatory
proteins in the upper arms are taken out of the chain and inserted into an intake port. Information contained in the molecular structures of proteins and DNA is compared to. Database of a larger nanocomputer that is external to the nucleus and is linked via a communications channel to the cell repair spacecraft. Any structural irregularities are fixed, and the proteins reattached to the chain of DNA [14,15] which coils back into shape. The repair vessel, which would have a diameter of just 50 nanometers, would be smaller than the majority of germs and viruses and be able to provide treatments and cures that are much beyond the capabilities of modern doctors. "Internal medicine" would become significant when a patient's blood stream had trillions of these devices. Diseases like arteriosclerosis and cancer virus infections might be eradicated since disease would be combated at the molecular level.

Nanomedicine:

Nanorobotics has potential uses in medicine, such as focused drug delivery and early detection. In the areas of biomedical instruments, surgery, pharmacokinetics, diabetes monitoring, and cancer delivery, future medical nanotechnology is anticipated to use injectable nanorobots to deliver medicine at the cellular level. Such nanorobots should not be able to replicate, since this would needlessly increase device complexity, decrease reliability, and obstruct the medicinal mission [16,17]Rather, it is proposed that medical nanorobots would be produced in fictitious, meticulously regulated nanofactories, where nanoscale machinery would be firmly incorporated into an imaginary machine that would produce macroscopic goods.

Disadvantages:

1) Initial design cost is very high.

2) The design of the Nano robot is a very complicated one.

3) To Interface, customize and design and is complex.

4) Privacy is the other potential risk involved with Nano robots. As Nano robot's deals with the designing of compact and minute devices, there are chances for more eavesdropping [66-68] than that already exists.

5) Systems can create stray fields which may activate bioelectric-based molecular Recognition systems in biology. Electrical Nano robots are susceptible to electrical Interference from external sources such as RF or electric fields, EMP pulses [68], and Stray fields from other in vivo electrical devices [15].

6) Nano robots can cause a brutal risk in the field of terrorism. The terrorism and antigroups can make use of Nano robots as a new form of torturing the communities as Nanotechnology also has the capability of destructing the human body at the molecular Level.

7) The idea of introducing small submarines through the blood vessels has been captured in many films. But the blood at nanoscale becomes viscous and sticky fluid which does not let the submarine to drive along the vessels. Another phenomenon that would not let the Submarine to travel is the Brownian movement of the molecules; the collisions between Molecules are incontrollable and unpredictable [1-3]. In the last decade, progress in developing nano sized hybrid therapeutics and drug delivery systems has been used for biomedical applications. These machines are expected to be highly efficient, controllable.

Key fundamentals of nanorobots in the treatment of cancers:

As a miniature structure, nanorobots are capable of executing predetermined missions and bear stark differences to their macro scale robotic counterparts. The primary challenges in the development of nanorobots or nanomechanical components lie in their construction and control. These devices operate within a microenvironment that exhibits physical characteristics distinct from those encountered by conventional components. The composition and structure of nanorobots are not uniform and can vary depending on their intended function and the materials and technologies utilized in their creation. The field of nanorobotics is an ever-evolving one, with ongoing advancements and breakthroughs. In this regard, we have presented a general outline of some of the crucial components and structures commonly found in nanorobots currently, most nanorobot experiments are conducted under conditions akin to those found in human microenvironments. To ensure that nanorobots can effectively eliminate cancer cells within the human body, scientists have set stringent standards for their fundamental design elements. It is noteworthy that medical nanorobots are still in the nascent stages of development and are yet to be widely implemented in medical treatments. The specific composition and structure of these devices may greatly vary based on their intended application and the necessary requirements for safety, efficacy, and scalability.[14]

Table 1: Overview of some key components and their structures of medical nanorobot.

Component	Description	Structure
Shell	The exterior casing of th medical nanorobot, whic is designed to b biocompatible with th human body. The materia used for the Shell can vary but common option include silicon, carbon, an diamond.	The structure of the shel plays a crucial role in th performance and safety of nanorobot. For instance, smooth and spherical shel design reduces friction an decreases the likelihood o causing damages t surrounding tissues. On th other hand, a rough an irregular shell design ca enhance the nanorobot' ability to attach to target a cancer cells or tumo tissues. The shape, size, an surface features of the shel can be optimized fo specific applications.
Power source	Medical nanorobots nee an energy source t function. This can be in th form of a battery, hydroge fuel cell, or even energ derived from the body' metabolism.	The integration of th power source into th nanorobot's design ca greatly impact it performance, stability, an safety. The power sourc can be embedded within th shell or attached to th surface as an externa component. The size an placement of the powe source must be considere to ensure optima functionality.
		The payload of a medica nanorobot can be

Payload	This refers to the specifi function that a nanorobo was designed to perform such as targeted drug delivery, imaging, or tissu repair.	Integrated within its shell o attached to its surface as a external component. Th type and the amounts o payloads required wil depend on the intende application and th requirements for efficac and safety. For instance, a nanorobot designed fo drug delivery may have a payload of drugs o therapeutic agents, while a nanorobot designed fo imaging may have a payload of imaging agent or contrast agents.
Sensors	These are devices that allow nanorobot to detect changes i the body, such as temperature pH, or the presence of specifi molecules.	Sensors can be placed o the surface of a nanorobo or integrated within it shell. The type and th number of sensors require will depend on the intende application and th information necessary fo effective operation. Fo instance, a nanorobo designed for imaging may have sensors to detect light o local oxyge concentrations, while a nanorobot designed fo drug delivery may hav sensors to detect specifi biochemical signals, such as pH, GSH concentrations etc.

Actuators	These are devices that enable the nanorobot to physically interact with the body, such as moving through the bloodstream, releasing drugs, or performing surgery.	Actuators can be placed on the surface of a nanorobot or integrated within its shell. The type and number of actuators required will depend on the intended application and the actions necessary for effective operation. For instance, a nanorobot designed for drug delivery may have actuators to release drugs in response to specific local signals, while a nanorobot designed for surgery may have actuators to manipulate tissues or remove debris.
Communications	Medical nanorobots may need to communicate with each other or with external devices, such as an antenna of a computer or a remote control system.	Communications can be achieved through various means, such as wireless signals, electromagnetic wave signals, or physical connections. The type and range of communication required will depend on the intended application and the requirements for coordination and control. For instance, a nanorobot designed for imaging may communicate with a computer to transmit images, while a nanorobot designed for drug delivery may communicate with other nanorobots to coordinate

		The release of payload drugs.

Some typical examples of medical nanorobots:

Table 2

Nanorobots type	Key characteristics	Ref
1) Pharmacytes	A medical nanorobot with diameter of 1–2 µm Molecular indicators o chemotactic sensors are used t ensure the precision of th targeting system They can be eliminated o recuperated through centrifug nanapheresis after finishing the	[52]
2) Microchips	Nanorobots possess microchips which can conduct current signals once the molecules detect a disease The benefits are the smal charge to yield and simple t operate	[53]
3) Respirocyte	A type of nanorobot that carries oxygen like an artificial red blood cell The power is achieved throug endogenous serum glucose	[54]
4) Microbivores	The nanorobot is flat an spheroidal in shape fo nanomedical uses With diameter of 3.4 µm along it main axis and a diameter of 2. µm on the minor axis It has th phagocytic capability which i almost 80-fold higher proficien than other macrophages	[55]

5) Clotocytes	They have the ‘instant hemostasis biological activit which is called artificia mechanical platelets They als transport substances that assis in the coagulation process.	[56]
6) Chromallocyte	The renovation machine wil first assess the condition b inspecting the cellula substances, actions, and works These repair machines ar capable of overhauling th complete cell.	[57]

Materials of Nanorobots:

At nanometer scales to work within tumor tissues and cells, the primary consideration for the design of nanorobots was the biocompatibilities of materials. The first challenge encountered in designing a nanorobot to perform medical tasks is the issue of materials science or surface science, since the operation of a microrobot is largely dependent on the properties of its surface and materials. The molecular interactions among biological species and the surfaces of a nanorobot drastically affects the motion control of a nanorobot in a biological microenvironment. Nanorobots are mostly made of biocompatible or biodegradable materials. These biodegradable materials are able to dissolve or disappear at the end of their tasks. Meanwhile, they should be able to accomplish a wide range of accurate tasks including 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, etc. [15,16]These materials should also be flexible and deformable to ensure workability and mechanical properties of nanorobots to work in the human biological microenvironments.[17,18] need to be more maneuverable in three dimensions, in viscous and elastic body fluids, as well as in phantom organs. Besides, when designing nanorobots to perform adaptive tasks in a variety of different biological environments, stimulating-responsive materials becomes significant important.[19]

Types of driving forces for nanorobots in cancer drug delivery:

Drug delivery is becoming one of the most common uses for nanorobots in cancer therapy as nanotechnology advances. Several distinguishing characteristics of nano-drug carriers have been created, such as their small sizes, high specific surface area/internal void volumes, and exceptional physicochemical qualities. Generally speaking, an ideal nanorobot has certain unique qualities like guided navigation, tissue penetration, propulsion, cargo transportation, and release. Apart from the constraints imposed by passive mass transport, the majority of drug delivery nanocarriers currently in use are dependent on systemic circulation and do not possess the selfdriving force and navigation capabilities necessary for targeted distribution and tissue penetration. It has been claimed that a number of anti-tumor therapies employing Nano robots allow for precision therapeutic drug delivery to specific tumor regions.[20,21] Through intravenous injection, malignancies could be treated by nanorobots. When administered intravenously (IV) or orally, nanorobots can be utilized to treat cancer by aggregating at the site of the tumor to enhance the anti-cancer effect while causing minimal damage to healthy, normal cells. A plethora of cutting-edge technologies have been developed to assist nanorobots in reaching the sick locations in order to precisely deliver the therapeutic payload straight to the tumor area.

External magnetic-driven nanorobots:

Several exploratory investigations have been conducted to validate the characteristics and transport function of nanorobots driven by magnetic fields [22,23] Research on using nanorobots to cure cancer has also produced a number of outstanding results. The ability of magnetic helically structured nanorobots to be driven by rotational-to-translational motion using a torque produced by an external magnetic field is a requirement for this driving force pattern. [24,25] A multi-component magnetic nanorobot was constructed by Andheri et al.[26] and made from multi-walled carbon nanotubes (CNT) that were loaded with anticancer antibody and doxorubicin (DOX). When stimulated by intracellular H2O2 or local pH changes, this selfpropelling magnetic nanorobot may release anticancer drug payloads inside three-dimensional (3D) spheroidal tumors. It could be propelled by an external magnetic field in complicated biological fluids microenvironments of tumors. The nanorobot, which was made of magnetic Fe3O4 nanoparticles that were chemically conjugated, was able to release DOX preferentially into the intracellular lysosomal compartment of human colorectal cancer (HCT116) cells by opening the Fe3O4 nanoparticles' surface gate. A nickel-silver nanoswimmer that could be driven by an external magnetic field and deliver micronized particles at speeds greater than 10 μm s−1 was described by Wang et al. [27].

This modified polymer microsphere, consisting of poly (D, L-lactic-co-glycolic acid) (PLGA), was combined with doxorubicin. The robot's expanded polydimethylsiloxane (PDMS) channel allowed it to administer drug-carrying microspheres while being driven by a flexible magnet. The drug-carrying microspheres were discharged to destroy the human cervical cancer (Hela) cells when the nanoswimmer got close to them.

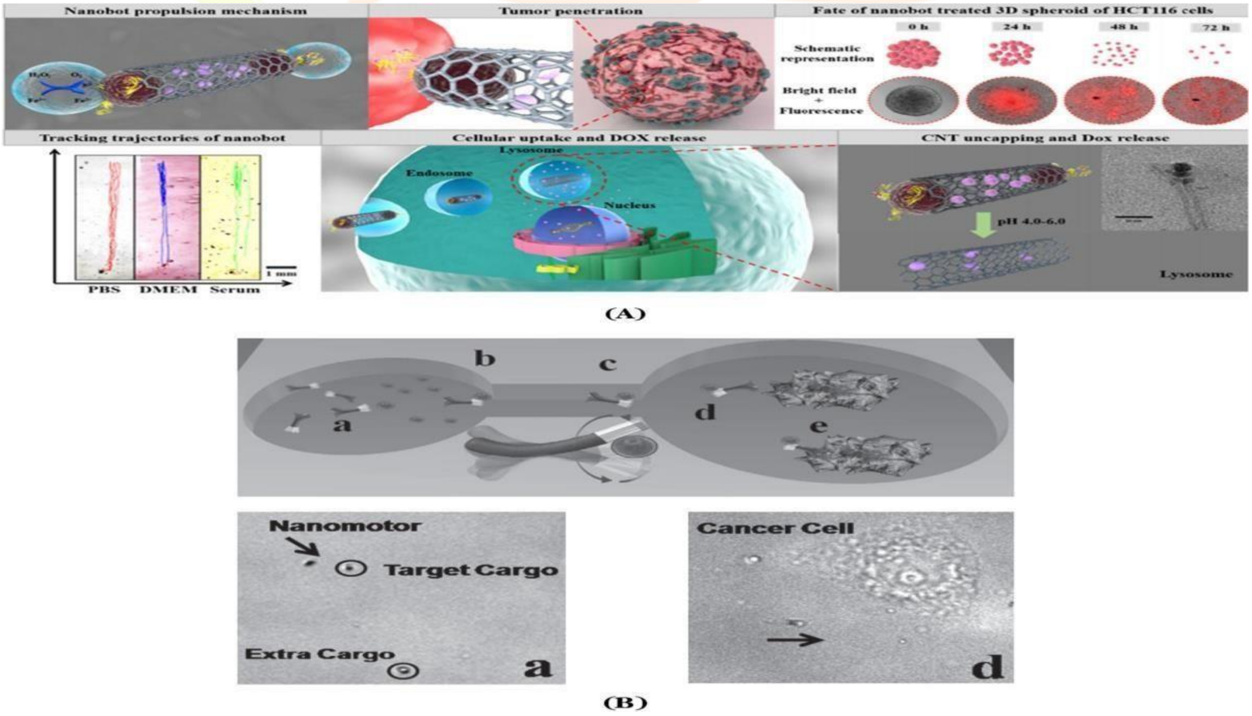


Fig.2 A Illustration of a DOX-loaded magnetic nanorobot which was driven to penetrate into the 3D spheroid tumor, followed by drug release under intracellular endo/lysosomal conditions. Modified and reprinted from ref. Reproduced with permission, Copyright 2020, Springer
Nature.
B. The process for flexible magnetic nickel-silver nanoswimmer capturing magnetic polymer
Particles loaded with drugs and transporting it to target cells via channels. Modified and reprinted From ref. Reproduced with permission, Copyright 2011, Wiley–VCH

Using a biological template approach, pine pollens were converted into a magnetic microrobot. Doxorubicin was then vacuum-loaded into the robot's natural cavity, and the medication was uploaded through the PDMS narrow channels by the microrobot's cooperative behavior. When the semi-natural magnetic microrobot reaches the interior of the cancer cell, it releases the payload drug molecules to kill the cell by creating fluid inside the cavity with its magnetic rotor. Anti-tumor drug delivery and bacterial flagella motion imitation using an external magnetic field are common applications for field-driven nanorobots.[28,29] Drug-loaded nanoliposomes can be successfully delivered to hypoxic areas within bio hybrid micro robots (based on Magnetococcus marinus strain MC-1) by means of an external magnetic field, according to research by Felfoul et al.In these natural settings, bacteria are used to swimming along the living region's magnetic field lines to low-oxygen locations. Up to 55% of the micro robots could enter the anoxic area of tumors in the HCT116 large intestine in a xenograft mouse model when the drug-containing nanoliposomes were attached to MC-1 bacteria and given to mice with xenogeneic neoplasms while being guided by an external magnetic field. The microrobot showed superior tumor penetration capability in xenografts as compared to passive reagents.

External ultrasound driven nanorobots:

The establishment of an acoustic situation is not too difficult. Sound waves can travel through solid, liquid, and air media and can enter biological tissues deeply to power nanorobots from the outside without causing obvious harm to humans. On the other hand, using ultrasound might cause oxidative stress in the cells, which could affect target tumor cells as well as healthy cells [30,31]The fundamental process is that the surface of asymmetric nanorod-nanorobots experiences a localized acoustic streaming strain from the ultrasonic wave, which creates a driving force for the movement of the nanorobots. High-intensity focused ultrasound has the potential to drive tubular nanorobots in a flexible movement condition and to produce rapid evaporation of chemical fuel. These tiny robots with tubes for legs could move at a very rapid pace and enter tissues with a powerful driving force. Garcia et al. demonstrated how nearinfrared light-triggered drug release may be achieved by using ultrasound-driven nanowire motors to deliver drugs to HeLa cancer cells quickly. In this instance, it was found that within 15 minutes of NIR light irradiation, 38% of the DOX payload medication was released inside the cancer cells.

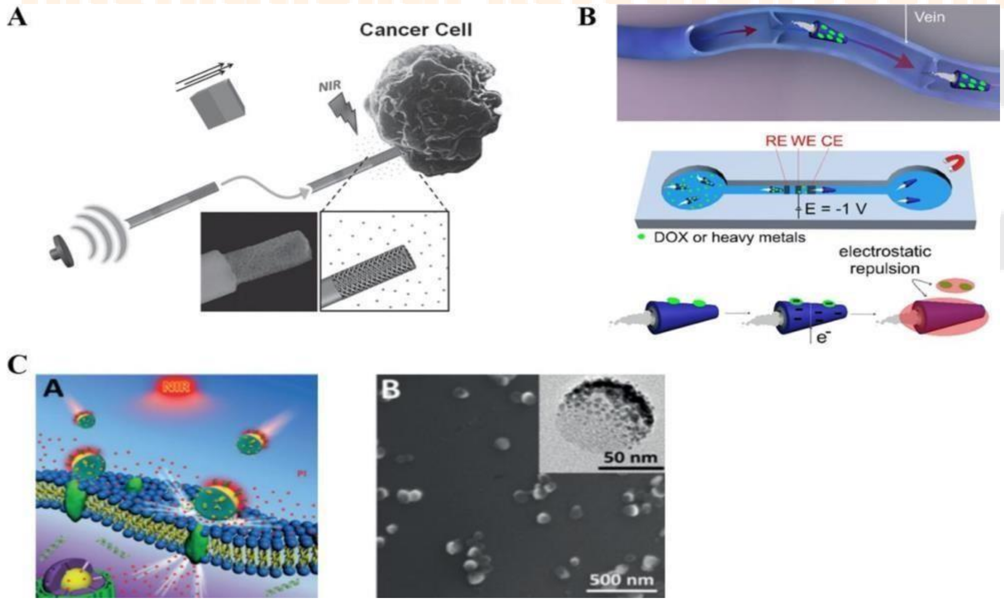


Fig 3 A Schematic of the nanowire motor which was driven by ultrasound toward cancer cells, followed by NIR light-triggered drug release. Modified and reprinted from ref. Reproduced with permission. Copyright 2014, Wiley–VCH. B The illustration of the Bi-based tubular microrobot showing the performance for smart drugs or heavy

metals delivery in vein with electrochemical release mechanism. Modified and reprinted from ref. Reproduced with permission. Copyright 2019.

Biological-driven nanorobots:

Bio-driven micro robots or nanorobots primarily refer to bio hybrid micro robots. They are created from live microorganisms (cells) and artificial materials. Microorganisms, such as sperm and bacteria moving under the propelling effect of flagella, could act as an engine for bio hybrid micro-/nanorobots. Besides, sperm, which has the special ability to bind with body cells, could significantly raise the issues of biocompatibility and safety of micro-/nanorobots. It was reported that a bio hybrid robot having a 3D printed magnetic tubular microstructure and four arms adopts a mobile sperm cell as its power source and drug carrier. As compared to entirely synthetic micro robots or other nanocarriers, such kind of sperm-hybridized micro robots could seal high concentration drugs into sperm membrane and protect the payload drugs from being diluted by body liquid or affected by enzymatic degradation.

Hybrid-driven nanorobots:

Numerous studies have confirmed that employing a hybrid power source, nanorobots may successfully distribute drugs in a targeted manner. It has been demonstrated that nanorobots have potent binding properties toward toxins and pathogens, which enable them to have good detoxification capabilities.[32] He and colleagues used layer-by-layer self-assembly technology to construct a tubular multi-layer microrobot. These microrobots can deliver doxorubicin to cancer cells at up to 68 microns/second thanks to a combination of bubble driving and magnetic field guidance. Nanorobot mobility could be regulated by the magnetic field in addition to conventional physical power sources. For example, Wang’s group at the University of California used an electrode position approach to create porous metal rod-like nanorobots.[33]Their nanorobots’ porosity nature allows them to carry more medicinal molecules—twenty times more than a homologue made of planar metal. The nanorobots' drug release was triggered by nearinfrared (NIR) light. The medications that were discharged effectively killed tumor cells under the guidance of an external magnetic field and an ultrasonic sound. A. hybrid magneto-electric nanorobot designed by Chen et al. was able to distribute drugs in a targeted manner by releasing the drug in response to an external magnetic field. Victor et al. created a three-segment Au-NiAu nanowire motor that was directed by a magnetic field and could be driven by ultrasound. The ultrasound-propelled particles can move in any direction by changing the direction of the applied magnetic field. Recent research has demonstrated the intriguing potential of bismuth (Bi) compounds for biological applications.

Can We Use Nanobots to Cure Cancer?

Oncology:

Nanobots have the potential to be used for cancer diagnosis and treatment. Scientists have been experimenting with using nanobots to actively seek out and destroy cancer cells, according to a paper published in IFL Science. According to the 2012 design, the nanobots would patrol the bloodstream and search for indications of distress, much like white blood cells. The robots will discharge a tiny but lethal cargo of chemicals or nanoparticles when they identify a target cell. The cancer cells would therefore be forced to self-destruct as a result of these nanoparticles interfering with their ability to proliferate. Targeting only the tumor cells and ignoring healthy ones is possible with this kind of precision therapy. This holds significance as it has the potential to mitigate the adverse effects of chemotherapy. Scientists introduced nanobots into the blood components of the participants. In order to stop the blood flow to the cancerous tumors, the nanobots entered the bloodstream, found the blood arteries surrounding the tumors, and delivered blood clotting medications. The study found that the treatment was effective in reducing the size of the tumors and preventing their spread.

Challenges faced by nanorobots for clinical cancer Treatment:

. Because they can more precisely target cancer cells, minimize side effects, and enhance treatment outcomes, nanorobotics have the potential to completely transform the way we treat cancer. But before clinical cancer treatments can widely use nanorobots, there are still a lot of issues that need to be resolved. The technical complexity, precision, safety concerns, financial and resource constraints, regulatory issues, and scaling challenges that impede the development and application of nanorobotics in clinical cancer treatments will be covered in this section.

Technical complexity and precision

The development of nanoscale components, motion control, stability assurance, and other technical challenges must be overcome in order to design and operate nanorobots for therapeutic cancer therapies. The accurate control of magnetic nanorobots using externally applied magnetic fields is one of the main problems. The intricacy of magnetic fields in small places on a technical level Additionally, other electromagnetic waves' interference make it challenging to achieve precise and delicate control over the movements of nanorobots, which could lead to erroneous tumor targeting and possible damage to human tissues or organs. [35] Furthermore, the bodily fluid environment at low Reynolds numbers presents additional difficulties for nanorobots in terms of working accuracy and speed. The biological environment can have a significant impact on the precision and velocity of nanorobot operations. Moving proteins, red blood cells, and the interactions between immune cells and foreign particles can cause the movements and actions of nanorobots in blood to be retarded or even eliminated. Increased power conversion efficiency is required to facilitate nanorobot movements and actions in vivo. Urine and saliva are two more biological fluid types that must also be taken into account, in addition to blood. Diffusion and electrophoresis-driven catalytic motors will experience decreased efficiency and metal corrosion in both scenarios.

Safety concerns:

Concerns about the safety of nanorobots and their possible negative effects on humans are legitimate when it comes to their prospective use in biomedical applications, especially in cancer treatments. In addition to endangering patients, malfunctioning nanorobots may have unforeseen negative effects that make treatment even more difficult to administer. For instance, the use of tubular DNA nanorobots containing thrombin may prove inefficient in situations of malignant tumors characterized by poorly established blood arteries, eventually failing to meet the intended therapeutic goals. A comprehensive methodology combining extensive preclinical and clinical testing is necessary to solve these issues and guarantee the safety and effectiveness of nanorobots for cancer treatments. Such a method will aid in assessment. The nanoscale devices' biocompatibility, pharmacokinetics, and pharmacodynamics in diverse biological environments. Furthermore, putting in place strong quality controlled will be essential to take precautions during the production process to reduce the possibility of device failure and guarantee reliable performance amongst Nanorobot batches.[36]

Regulatory issues

The current absence of comprehensive regulations governing the development and the use of nanorobots may hinder their widespread adoption by both public and Private sector entities. Establishing appropriate regulatory frameworks that can effectively address the unique Challenges posed by nanorobotics, while simultaneously Promoting innovation and safeguarding public health, and is Essential for the successful integration of nanorobots into Clinical cancer treatments. Regulatory agencies should focus on developing guidelines that encompass the entire lifecycle of nanorobots, from design and development to clinical trials and postmarked surveillance. Such guidelines should also include Provisions for collaboration and data sharing among Researchers, industry, and regulatory agencies to ensure that all stakeholders can contribute effectively to the Development of safe and effective nanorobotic therapies.

Funding and resources

Developing nanorobotics for clinical cancer treatments is an expensive endeavor that necessitates substantial funding and resources, as well as specialized equipment's and Human expertise. Securing adequate funding for research and development is paramount to advancing the field of nanorobotics and overcoming the various challenges it faces. Government agencies, private organizations, and philanthropic institutions should collaborate to provide financial support for research initiatives and facilitate the translation of research findings into clinical Applications.

Moreover, fostering collaboration among researchers, Industry stakeholders, and regulatory agencies will be Instrumental in expediting the development of nanorobotics for cancer treatments. Such collaborative efforts Can help optimize resource allocation, drive innovation, and ensure that regulatory requirements are met, ultimately accelerating the translation of nanorobotic therapies from bench to bedside.

Scalability

Scaling up the development and production of large Numbers of nanorobots for clinical cancer treatments is a formidable challenge due to the complex and time-consuming nature of the manufacturing processes. Tis scalability issue involves several key aspects that need to be addressed, including production techniques, cost, quality Control, and supply chain management.

Production techniques:

Nanoscale device production is frequently not well suited for conventional manufacturing methods. Novel manufacturing techniques and technologies that can consistently build complex nanostructures with great precision are needed in order to mass-produce nanorobots. The development of technologies like self-assembly, 3D printing, and nanolithography may make it possible to produce nanorobots on a bigger scale. Furthermore, production might be further streamlined by incorporating automation and machine learning into the manufacturing processes, which would decrease human error and boost overall efficiency.

Cost:

One major obstacle to the widespread use of nanorobots is the expensive cost associated with their development and manufacturing. Both increases in manufacturing efficiency and advancements in nanomaterials will be necessary to lower production costs. The development of new, more affordable nanomaterials or the improvement of already-existing ones, for example, may contribute to a reduction in the overall cost of nanorobots. Furthermore, closer cooperation between scientists, producers, and financing organizations might encourage the creation of more economical production methods.

Quantity control:

Ensuring the safety and efficacy of nanorobots during mass production requires a strict adherence to quality control standards. This involves creating thorough testing and validation procedures to find possible flaws and guarantee that nanorobots fulfill the required performance standards. By helping manufacturers to recognize and address problems during production more rapidly, the implementation of in-process monitoring and real-time feedback systems can further enhance quality control.

Supply chain management

The complexity of the supply chain for nanorobots will rise along with their production. Developing effective supply chain strategies that can manage the sourcing, storing, and shipping of nanoscale materials and components will be necessary to manage this complexity. To streamline the flow of materials and guarantee the prompt delivery of nanorobots to healthcare practitioners and patients, this may entail forming partnerships between manufacturers, suppliers, and logistics companies.

Other targeted cancer therapies:

- Various DNA Nanorobots

Since DNA-based nanorobots are naturally biocompatible and biodegradable, they have garnered a lot of interest due to their enormous potential for a variety of cancer therapeutic applications. Based on the well-known complimentary base pairing concept. To create the desired DNA, single-stranded DNA is folded repeatedly and stabilized by several short oligonucleotides known as "staple strands." Tiny-scale structures. The Targeting ability of DNA origami is introduced by its outstanding addressability, which enables additional functional ligands, biomolecules, or nanoscale objects to be precisely structured on a desired Position along its outer surface. A pre-programmed rectangular DNA origami nanorobot (20 nm x 30 nm) was created by Nanorobots et al. that was able to efficiently penetrate ovarian cancer cells and load Adriamycin. It has also been reported that ribonuclease (RNAse) molecules can be successfully delivered into cancer cells by DNA origami nanorobots. According to Singh et al., DNA origami technology can bend a single strand of DNA into the proper shape. To modify the molecular characteristics of DNA and enable precise binding of the tubular nanorobot to the receptor in vivo for the aim of site-specific treatment, chemical methods may be employed. Nevertheless, it is also thought that the DNA nanorobot might not be able to have a major impact on the treatment if the blood supply inside the tumor cells is still insufficient. One of the transmembrane EGFRs, HER2, is engaged in a number of different information-signaling processes that occur within cancer cells. Breast cancer's malignancy may be increased by HER2.Affected individuals always have a poor prognosis when the HER2 Receptor is overexpressed. A nanorobot dubbed HApt-tFNA was designed by Ma et al. to enhance its delivery and therapeutic efficacy in treating HER2-positive breast cancer with fewer side effects. He anchored an anti-HER2 inducer (HApt) to a tetrahedral Framework nucleic acid (tFNA).

The DNA framework smart DNA, which can specifically breakdown particular tumor proteins in cancer cells, is the foundation of the nanorobot's construction. Next, a mouse model was implanted with the DNA nanorobot. According to experimental findings, tFNA might increase the DNA nanorobot's stability and lengthen HApt's blood circulation period. Thus, HER2 could be more effectively driven into lysosomal degradation by hapt-tFNA. This innovative DNA nanorobot enhances the prognosis of patients with breast cancer and provides a new avenue for targeted protein breakdown in precision breast cancer treatment.

Photo thermal therapy

In order to trigger the apoptotic process in cancer cells, near-infrared light (NIR) can be absorbed by nanorobots and transformed into local thermal heat as a photothermal treatment with excellent spatiotemporal selectivity. Photothermal therapy is not yet developed, nevertheless, because tumor locations are not precisely and controllably targeted. Strong magnetic tri-bead microrobots loaded with drugs that respond to NIR light were created by Song et al., and they showed good biocompatibility even at concentrations of up to 200 µg/ml. In vitro experiments revealed that the ___14 micro robots exhibited fast NIRresponsive photothermal properties. The release of medicines by micro robots was initiated when the local temperature reached 50°C. Targeted chemotherapy combined with photothermal therapy has been successfully applied to lung cancer cells, and microrobots within microchannels may target tumor cells..[37]

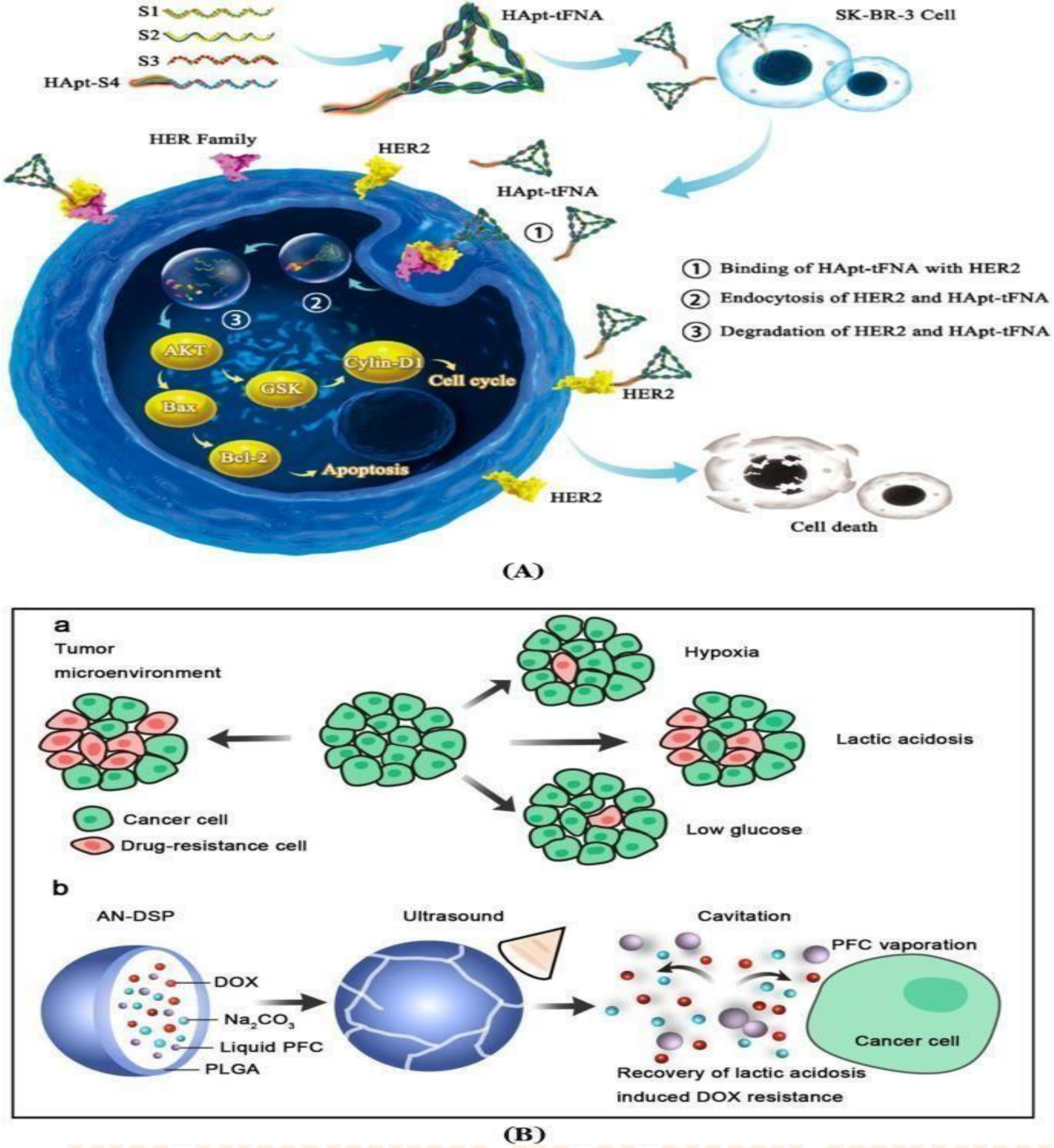


Fig.6

A Schematic illustration of the nanorobot HApt-tFNA incorporating HER2 in the HER2-HApt-tFNA complex and internalizing the complex into human mammary gland adenocarcinoma cells. The complex degrades within lysosomes, which suppresses cell proliferation and induces cell Death. Modified and reprinted from ref. [249]. Reproduced with permission. Copyright 2019, American Chemical Society. B The effects of the cancer Microenvironment on the development of drug resistance, and the ultrasound-responsive alkaline nanorobots (AN-DSP) for enhancing anticancer Effects Modified and reprinted from ref. [268]. Reproduced with permission. Copyright 2020, Royal Society of science and chemistry.

In vitro demonstrated the feasibility of nanorobotic targeted chemotherapy-photo thermal therapy in cancer.

Conclusion:

As previously mentioned, there is a growing body of research being done on the creation and use of nanorobots in cancer treatment. Material and artificial intelligence scientists should collaborate closely with medical researchers to conduct comprehensive studies of the behaviors and functionalities of nanorobots, including drug delivery, targeted therapy, minimally invasive surgery, tumor detection and early diagnosis, and other cutting-edge nanorobot-assisted comprehensive treatments, in order to fully realize the potential of nanorobots in the field of cancer treatment. Scientists should investigate the needs and challenges faced by oncology physicians and design medical nanorobots or nanosubmarines specifically targeted at cancer in order to expedite the translation of cancer research into practical applications. This is because recent in vitro and in vivo experiments have shown encouraging results.

We think that in the near future, it will be possible to use nanorobots as an integrated platform for various goals in many anticancer fields. The successful translocation of nanomedicines across a vascular barrier at the micron size is a prerequisite for the development of effective cancer treatments.The varied tumor microenvironment poses a hurdle to the efficacies of dynamically targeted nanomedicines in vivo, even if these treatments have exhibited great targeting efficiency on cancer cells in vitro[38]. Conversely, direct bloodstream exposure of vascular endothelial cells provides handy options for tumor blood vessel-targeted nanomedicine detection and function. It is essential to better optimize the tumor microenvironment responses and the selectivity of the pertinent targets.

The intricacy and diversity of tumor biology, the paucity of a thorough knowledge of the interactions between nanomaterials and biology, and the lack of mass production and scalable synthesis technologies for nanorobots and nanosubmarines all pose barriers to the clinical application of experimental nanorobots and nanosubmarines. The potential of precision drug delivery is demonstrated by the use of DNA nanotechnology in the form of DNA origami for thrombin delivery; nevertheless, significant obstacles including immunogenicity, in vivo metabolic behavior, and large-scale manufacture need to be addressed prior to practical adoption.[39 Future research must focus on selecting nanomaterials with proven biosafety and distinct in vivo metabolic behavior, regulate drug uptake by modifying pertinent target molecules, and delve deeper into understanding the mechanisms underlying interactions between nanorobots and nanosubmarines and proteins, cells, tissues, and organs. Additionally, the expansion of nanorobot clinical applications requires sophisticated characterization systems and preparation techniques. It is anticipated that in the future, basic structural medical nanorobots will develop into more advanced, multipurpose medical devices that can eventually become real nanosubmarines in the bloodstream.

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