Review on: Micro/Nanorobot for targeted drug delivery

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School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

The thesis/project titled "Review on Micro/Nanorobot for targeted drug delivery system" was submitted by Tania Rahman. 17146065 of spring, 2017 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 20.11.22.

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Ethics Statement

No animal or human trial was conducted during this study.

Abstract/ Executive Summary

Micro/nanorobot research has gained popularity in recent years. It has enormous promise in medical therapy since it may be used in targeted medication delivery, surgical procedures, illness diagnostics, and so on. Unlike traditional medication distribution, which depends on blood circulation to reach the target, the developed micro/nanorobots can move independently, allowing pharmaceuticals to be delivered to difficult-to-reach locations. Nanorobots can be driven by endogenous and exogenous power. There are also cell-driven and DNA origami nanobots. In this review paper, I will discuss the approaches of nanobots, their mechanism, and their application in various medical fields. As well as their limitations and future perspectives.

Keywords: micro/nanorobot; nano-medicine; targeted drug delivery; exogenous power; endogenous power; cell-based micro/nanorobot and DNA origami.

Dedication

Dedicated to the immense support of my parents, and to my instructors.

Acknowledgement

First of all, I want to thank Almighty Allah for giving me the strength and the capability to complete the whole project.

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List of Acronyms

DNA Deoxyribonucleic Acid

EPR Enhanced Permeability and Retention

ABF Artificial Bacterial Flagella

UV Ultraviolet

3D 3- Dimension

SiRNA Small interfering RNA

mRNA Messenger RNA

NIR Near Infrared

MSNs Mesoporous Silica Nanoparticles

RBC Red blood cell

QDs Quantum Dots

Dox Doxorubicin Hydrochloride

MNPs Magnetic nanoparticles

CD45, CD3, and CD8 Receptors

WBC White blood cell

HIV Human immunodeficiency virus

AIDS Acquired immune deficiency syndrome

BGLs Blood Glucose Levels

SGLT3 Human sodium-glucose cotransporter type 3

GABA Gamma-aminobutyric acid

PFTs Pore-forming toxins

pDNa Plasmid DNA

ROS Reactive Oxygen Species

Chapter 1

Introduction:

In the world of pharmaceutical research, precise delivery of drugs technology has always been a source of concern. The ideal situation is for a therapeutic amount of a medicine to be delivered instantly to the prey organs/tissues/cells to create a significant impact, but this cannot be accomplished by regular administrative techniques. Most medications rely on body fluid flow to get about once they've been injected or consumed. Professor Daniel Ahmed, who heads the Acoustic Robotics Systems Lab at ETH Zurich in Switzerland, explained,"'If you inject particles into the body, they will follow the blood". As a result, some diseases may be difficult to adequately treat in this manner (Wild, 2021). Because of its increased permeability and retention (EPR) effect, tumour tissue is appropriate for medication administration. The EPR effect is advantageous for the the accumulation of specific-size molecules permits passive targeting nanodrugs to be directed to the tumor area. Actively targeted nanoparticles were connected with a variety of targeting ligands that were chosen based on the gene presentation differences between prey and regular cells. Nanoparticle aggregation increased lesser than double in tumour tissues as it did in regular tissues. The actively targeted nanoparticles are unable to identify and approach receptors in tumour tissues. This is not an excellent summary of current targets; Blood circulation through the target location is the sole source of enrichment at the target site. A drug delivery system must have certain abilities in order to deliver therapeutic payloads accurately. Micro/nanorobots are broadly utilized in medicine; Their duties include auxiliary operations, medical diagnostics, and medicine administration. In contrast to the conventional mode, which depends on blood supply to get to the desired location, micro/nanobots can move autonomously. This enables us to distribute regulated nanoparticles to hard-to-reach locations. The current drug - delivery method is based on blood circulation and does not have the navigational capabilities necessary for precise distribution (Hu et al., 2020). Nanorobots are designed to be drawn selectively to damaged cells, allowing for direct therapy of those cells while boosting efficacy, reducing adverse effects, as well as general improvements in public healthiness(Jahangirian et al., 2017). This is a device that can be seen under a microscope and has nanoscale dimensions. Certain devices are significant in primary healthcare applications (Nerlich, 2008).

1.1 Aim of the study

This study aims to provide an overall idea about nanobots in the sector of medicine and this review paper focuses on the approaches/composition of nanobots, their mechanism, their application in the various medical fields, limitations, and future perspectives.

1.2 Objective of the study

The objective of this paper is to determine its efficacy and its contributions toward targeted drug delivery or targeted fishing and various medical fields. The study also focuses on the mechanism and composition of these nanobots so that they can be improved by overcoming shortcomings and can be used in other possible applications in the future for more medical efficacy.

Chapter 2

Methodology

Based on certain recent and well-known research papers and articles from high-impact journals, this review, which intends to discuss nanobots in the medical sector for targeted drug delivery, was completed. An in-depth investigation was carried out through official reports, peer-reviewed publications, and articles. Impactful information was gathered from them using search engines including Research Gate, PubMed, Google Scholar, Science Direct, Elsevier, and others. Google search was further used to get fundamental data from reliable and significant websites. Finally, a careful screening of those articles was done to extract the most recent and relevant material to provide the best quality review.

Chapter 3

Nanobots

Nanobots are tiny robots that have a 50-100 nm width and perform highly particular tasks. They work incredibly well for medication delivery. Drugs typically travel throughout the body before they reach the site of the disease. The medicine can be precisely targeted using nanotechnology, increasing its effectiveness and lowering the likelihood of any negative side effects. The blood sugar level may be monitored using specialized sensor nanobots that are put into bloodstream beneath the tissue. These chips are made of biomolecules and are made to generate an electric signal. The internal drug-filled unit is typically 50–100 nm broad, and with drug carriers having walls only 5-10 atoms thick. Narrow wires embedded in their surface generate an electric pulsation when they notice illness symptoms, which causes the walls to crumble and releases the medicine. The simplicity with which the electrical pulse may be managed to control the amount and timing of medication release is a major benefit of utilizing nanobots for drug delivery. The walls are also easily biodegradable and hence safe for the body. It can also be used to repair or notice injuries and disorders inside the body. The medicine can also be directly aimed using nanotechnology, increasing its effectiveness and lowering the likelihood of any negative side effects. These nanorobots may one day be trained to treat certain damaged cells, acting like antibodies in our body's natural healing processes (Mehta & Subramani, 2012).

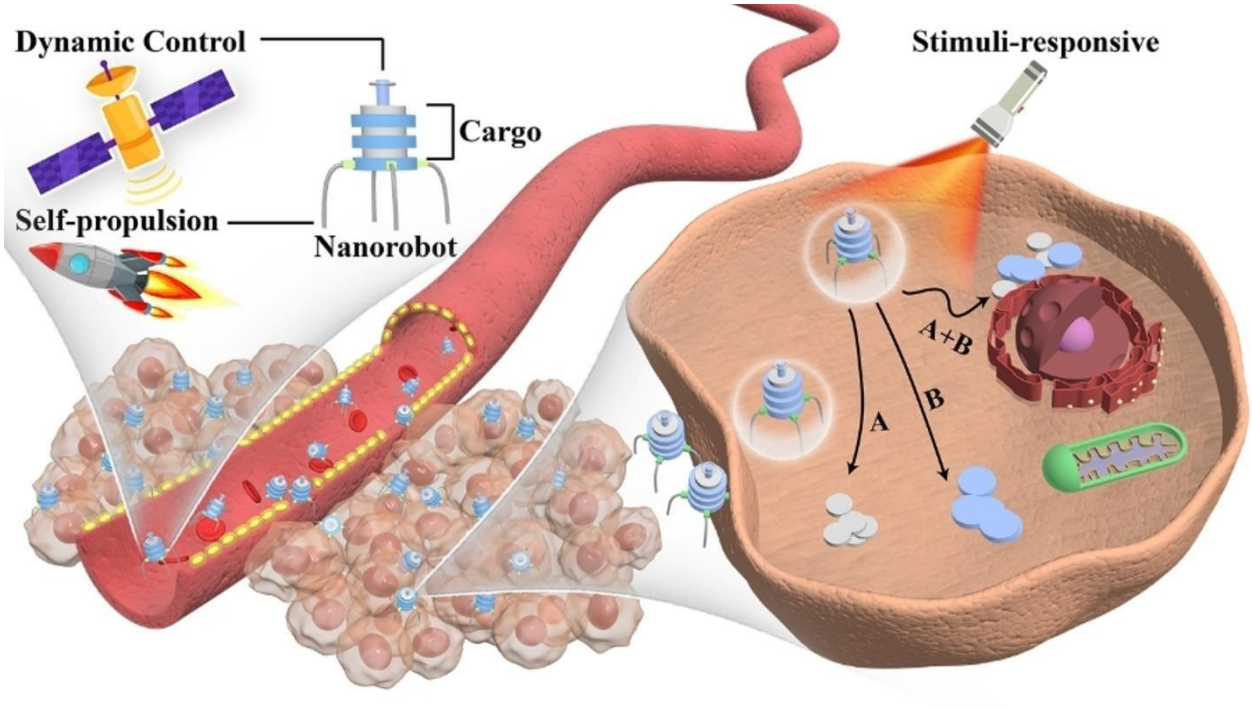

Figure 1: Nanorobots working on a tumour cell (Huang et al., 2021)

Chapter 4

Composition/Approaches of Nanorobots:

4.1 Exogenous Power-Driven Micro/Nanorobots:

Drug delivery robot systems must defeat Brownian motion since they are only micro- or nanoscale in size in order to achieve autonomous mobility in intricate bodily fluids. External power is often linked to the micro/nanorobot to coordinate its actions and drive the motion of the particles. Frequently used as an external power in drug carriers include magnetic field, electric field, light energy, acoustic wave, and heat energy. During the design process, a variety of transportation is frequently combined to create micro/nanorobots with a variety of capabilities (Hu et al., 2020).

4.2 Micro/Nanorobots Propelled by Magnetic Fields:

The typical design for magnetic propulsion is a flexible or helical swimmer. Through a torque produced by external magnetic fields and their helical structure, magnetically shaped micro or nanorobots are capable of being pushed and realizing rotational-translational motion. Two components make up the microrobot model created by Qiu et al. Under rotating magnetic fields, titanium-coated ABFs could navigate fluids in three dimensions with extreme accuracy, and the outer temperature-sensitive liposomes could discharge drugs when the temperature was controlled. A rod-shaped construction with segment splicing characterizes an adjustable magnetic nanorobot, and the adjustable joint in the centre is frequently constructed of silver. Jiang et al. created magnetic nano swimmers with 1, 2, and 3 links and investigated their motions in a magnetic field (Hu et al., 2020).

The findings showed that in 1- and 2-link nano swimmers, an antisymmetric motion was seen, while in 3-linked ones, an S-like motion was seen. Combining drug carriers can achieve active drug delivery based on these adaptable architectures. The ability of the nanomotor to move will depend on the size ratio of drug-loaded materials to the nanomotor in such a configuration. accurate placement, adjustable orientation, and a broad spectrum of movement of magnetic energy-propelled micro/nanorobot benefited. To carry out drug delivery, Sun and colleagues conducted a pine spore micromotor with two open-air sacs containing Fe3O4 magnetic atoms and medications. (Hu et al., 2020).

It is secure for magnetic field-driven nanorobots to operate in relatively mild magnetic fields. However, the metal added to the base material or the surface coating will restrict in vitro use. Metal trapped in vivo, for instance, may cause the human body to respond in an inflammatory or immunological way, among other ways. Alternative materials that are more secure and non-toxic are required (Hu et al., 2020).

4.4 Micro/Nanorobots Propelled by Electric Fields:

Electric field-powered micro/nanorobots are also rather widespread. A Janus colloidal design powered by both electric and magnetic energy, as well as several other systems that mix the two,

have been described. Although electric and magnetic forces are normally independent, they can be mutually changed into one another under specific conditions. Scientists have demonstrated micro/nanorobots' exceptional capacity to remove, carry, discharge load, and guide motion in vitro, laying a stable basis for medication administration applications in vivo. Although electrical power is widely accessible, its transmission is not as deep as that of a magnetic force, increasing the strength of the electric field in real usage. In practical applications, the harm produced by high currents to the human body should be considered (Hu et al., 2020).

4.5 Light Energy Propelled Micro/Nanorobots:

The nanorobot may go in any direction by modifying the light frequencies, polarisation, intensities, and propagation direction. By merging two trans-polarization nanomotors, Zhan and colleagues built synthetic swimmers; their motion can be controlled by varying the polarity orientation of the incident light. This concept might be useful for focused medicine delivery. Light energy may also function as a catalyst in generating redox reactions inside micro/nanorobots and propelling them forward by forming chemical gradients or bubbles. Wang et al. created a glucose-fueled Cu2O@N-doped carbon nanotube that potentially is initiated by viewable photocatalysis. It was non-hazardous, extremely biodegradable, and ecologically friendly, and it was capable of achieving exceptional motion and 3D motion control in physical environments. Despite outstanding results in vitro, its use in physical systems remains a difficulty due to the visible light's incapacity to permeate tissues. To counteract Brownian motion, an Au semi-nanoshell might produce thermal gradients and self-thermophoretic power. This technology was additionally covered with the membranes of a macrophage, which gave the nanorobot immunologic characteristics that allowed it to be fully involved in targeting and binding cancer cells. The driving ability of a photocatalytic TiO2-Au Janus micromotor activated by UV light was demonstrated. Light energy powered by nanorobots is intriguing, however, most existing research is done in vitro. When confronted with a complicated interior environment, it is worthwhile to investigate if its directed mobility can perform as well as in vitro for medication administration. Light energy will be used with various forms of energy to push the micro/movement of Nanorobots (Hu et al., 2020).

4.6 Ultrasound Energy Propelled Micro/Nanorobots:

Nanorobots propelled by ultrasound have enormous potential for active targeted medication delivery. Victor and colleagues. created an ultrasound-powered three-segment magnet-controlled Au-Ni-Au nanowire motor. The pressure gradient created by ultrasound caused its directional motion. The ultrasonic movement of nanoparticles assisted in the attack on malignant cells, also the release of burdened drugs was induced through NIR light stimulus. For intracellular siRNA delivery, a gold nanomotor was enveloped in a DNA strand capable of rolling circle replication and hybridization with siRNA. After only a few minutes of treatment, SiRNA operated like scissors, splitting the marked mRNA with a 94% suppression effectiveness. Ultrasound can give nanorobots powerful propulsion to overpower hurdles created in the complicated atmosphere of the patient's body. Nonetheless, the use of ultrasound may produce stress in cells, which may harm regular cells in addition to those targeted by nanotechnology (Hu et al., 2020).

4.7 Micro/Nanorobots with Endogenous Power:

The ability of nanorobots to drive themselves is mostly created by biological or chemical reactions. This sort of micro/nanorobot is usually asymmetrical, also it is frequently covered with a catalyst to get constant chemical fuel via its surroundings. The most common approach was a hydrogen peroxide decomposition process. The size of Janus fragments is nano- or micron-scale which have a distinct arrangement and design in each of their two semicircles.

Nanorobots were propelled by nonhazardous fuels such as glucose and urea. Urease was utilized as a catalyst to help urea decompose into carbon dioxide and ammonia. The way the robot's movement is reversed by the gas created by the chemical process is appropriate for the conditions of the digestive organs. A few flaws remain in the chemical energy-powered autonomous nanorobot, such as the difficulty in controlling its movement direction. One of its shortcomings is the inability to move continuously. Another significant barrier to its utilization in organisms is the security of the "fuel" and reaction by-products(Hu et al., 2020).

4.8 Other types of nanorobots:

For targeted medication delivery, RBC, microbes, and bone marrow are examples of cell-based micro/nanorobot systems that are expected to be efficient and compatible. Magneto-aerotactic bacteria is another prevalent kind. Shao and colleagues created hybrid self-guiding micromotors out of chemotaxis-capable neutrophils and loading-capable mesoporous silica nanoparticles (MSNs). The RBC microrobot may move and deliver medications over defined pathways while carrying Dox, quantum dots (QDs), imaging agents, and MNPs. DNA origami nanorobots are constructed from a single strand of DNA that has been folded repeatedly and is held together by several short oligonucleotides.

DNA origami offers a lot of potential in the realm of clever medication delivery. It enables items to be precisely grouped on the appropriate place of their surface, enhancing aiming ability. Li et al. produced DNA origami, a novel method that, if infused with adriamycin, successfully penetrates ovarian malignant cells (Hu et al., 2020).

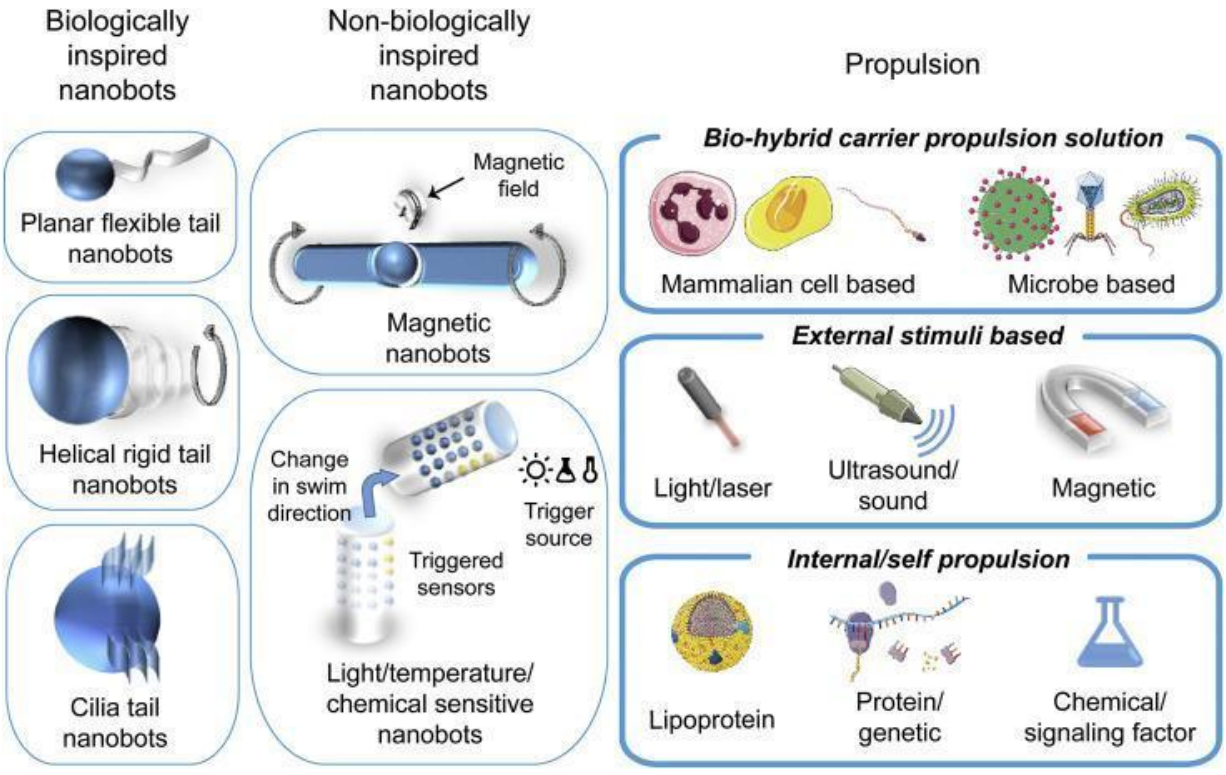

Figure 2: different types of nanobots. (Agrahari et al., 2020).

Chapter 5

Construction And the Mechanism of Nanorobots:

The study and development of drug-transporting nanorobots are not unknown. Scientists have already developed nanobot prototypes by employing powerful molecular design tools to produce nanostructures capable of storing diverse chemical payloads.
Researchers have successfully modified DNA to create precise forms and even instruct the 3-D DNA constructs to perform simple robotic functions, such as connecting to other cells and functioning inside other DNA material, using a technology known as 'DNA origami,' It was developed in 2006 by American scientist Paul Rothemund of Caltech University (Khulbe P, 2014). Nevertheless, the DNA nanorobots created therefore faced trouble moving, initiating, and focusing drug release. Although DNA nanorobots have before been created to interact with other nanorobots and move items, this is the first instance in which sophisticated computer skills have been utilized to assure the distribution of medication to certain sick cells (Khulbe P, 2014).

Rather than constructing a solo complicated chemical compound to recognize various aspects of a cell body, Dr. Stojanovic and his coworkers from Columbia adopted an alternative and possibly simpler, strategy founded by multiple basic molecules that make a robot in general.To detect a cell with three particular surface proteins, Dr. Stojanovic initially created three distinct molecular robot elements. Each component was made out of a DNA strand with two strands that were coupled to the antibodies that were precise to one of the outer proteins. The robot's antibodies attach to their proteins (CD45, CD3, and CD8) and function in harmony when these elements are introduced to a group of cells (Cerofolini et al., 2010).

A robot is operational in cells when each of the three parts is joined, and a further piece below with the designation 0 triggers a series of DNA strands reacting together. Every unit swaps a

DNA strand with another till the exchange is finished, at which point the final antibody acquires a fluorescently tagged DNA strand. After the chain reaction, which in a sample of human blood takes less than 15 minutes, only cells containing the 3 surface proteins are tagged with the fluorescent marker (Khulbe P, 2014).

The nanorobot prototype:

The researchers used the DNA computer program "Cadnano" to create a stretchable, 3-D hexagonal DNA nanorobot which can transport atomic "cargo" inside of its framework. Two DNA-aptamer "locks," also comprehended as nails, are included inside the foldable DNA gadget and wrap around the cargo to hold it safe until it reaches the target cells.

The atomic locks on the nanorobot are configured to react to certain essential protein combos on the cell membrane, allowing the payload to be delivered especially if the receptors on the designated cell contain the proper mix. "We can now combine sensing and analytical computar operations with complicated, however predictable, nanostructure some of the earliest hybridization of structured DNA, antibodies, aptamers, and metal atomic clusters were developed with the goal of targeting human cancers and T cells in a realistic, incredibly precise manner." Douglas stated (Wang, 2009).

A nano ‘smart box’:

Combining excellent structural design with DNA origami technology, the researchers developed a drug delivery system with two lock mechanisms, allowing the load to be secured inside the framework using a straightforward one-lock approach. According to Rothemund, who was not involved in the study, "the nanorobot proposed by Douglas... is a smart box' for other atoms — a box that opens if and only if it detects keys for locks placed on its lid. This implies that, for instance, if it is tuned to the proteins on the surface of cancerous cells, it could become a way to deliver medications to cancerous cells (and therefore only cancerous cells), possibly reducing overall adverse effects.(Amrute‐Nayak et al., 2009) and (Khulbe P, 2014).

"Because many different types of cells all have the identical 'keys' on their surfaces, whereas only the sequence of keys distinguishes them, this skill perhaps the sole method to recognize and supply medications to specific types of cells," he explained. "No strategy that I am aware of provides this kind of 'programmable medication supply" (Patel et al., 2006).

Chapter 6

Applications Of Nanorobots in The Various Medical Fields:

Nanobots are more imaginative and efficient in the critical diseases treatments and diagnostics such as cardiac arrest, diabetes, atherosclerosis, kidney stones, cancers and so on, due to the relatively low side effects and faster reaction time (Robert, 2009).

Nanobot applications in pharmaceuticals equip a unique set of tools for disease cure and improving the biological system of humans. Nanobots utilized in medicine include respirocytes, microbivores, clottocyes, pharmacytes, dentifrobots, and vasculoids (Freitas, 2007).

Detection and treatment of cancer: Nanobots have the potential to efficiently detect and cure cancer. Unlike traditional drugs, nanobots are very site-specific, meaning that they are engineered to recognize only damaged cells and operate on them, leaving healthy cells alone, and resulting in a minimal negative side impact. In the patient's body, tumour cells in the early stages of growth can be found using nanobots with biosensors (Sivasankar, 2012). According to Kumar et al. (2014), Salmonella bacteria have been genetically altered to carry miniature (3 m) robots called bacteriobots, that are steered to tumours by substances produced through malignant cells. They carry the medicine directly to cancer while leaving fit cells alone, which eliminates the negative effects of chemotherapy. However, the following bacteriobots can only identify the tumours of the breast and colorectal cancer. Also, nanobots can identify and cure various types of cancer.

This nanorobot may be tailored to various cell membrane receptors and the dosage can be released upon activation and may also be altered as needed. The nanorobot is constructed from synthetic Strands of DNA engineered to wrap into the requisite three-dimensional form (Dietz et al., 2009). The DNA nanobot's orientation shifts from sealed to tertiary after latching to the specific spot, allowing the stored therapy to be released (Douglas et al., 2012)

Murnane has revealed that nanobots limit blood supply to malignant cells and fight with them. Tumour cells cannot survive in the absence of blood flow, thus the researchers focused on this vulnerability. Nanobots are composed of a DNA sheet and thrombin, a blood-clotting enzyme. Thrombin works by searching for a protein called nucleoin on the tumour cell membrane. These nanobots release thrombin molecules, that initiate the clotting function, reducing the blood supply to the tumour and starving it (Murnane, 2018).

Neurosurgery: performing neurosurgery without any damage and injuries to the nerve and spinal cord is a big challenge. However, many approaches to optimizing and increasing nerve rejoining outcomes have been studied, including stimulating axon regeneration by development aspects and improved platforms. Trying to reconnect transected axons is a necessary stage in the repair process. Nonetheless, surgical technical limitations limit this (Chang et al., 2010).

A nano knife with a diameter of 40 nanometers has been created for axon surgery. Dielectrophoresis is useful in producing regulated axon movement inside a surgical area. The device can be produced via electrofusion, polyethene glycol, or laser-driven cell fusion.

In the discipline of neurosurgery, the most effective strategy to avoid morbidity and death is to treat cerebral aneurysms before they burst. Nanobots can be used to screen for potential aneurysms or to monitor existing aneurysms more closely. Cavalcanti et al. presented a concept for an intravascular nanobot capable of detecting aneurysm development by sensing elevated amounts of the nitric oxide synthase protein inside the injured blood artery. These nanorobots may be programmed to wirelessly send information about relevant vascular changes to healthcare practitioners, possibly lowering screening expenses for routine follow-up checkups and radiology (Saadeh, 2014).

Gene therapy: Pharmaceutical nanorobots can easily heal hereditary illnesses by analyzing the biomolecules of the cell's DNA and proteins to respect a reference structure (Sivasankar and Durairaj, 2012). A repair vessel created by assemblers floating inside of a cell's nucleus

conducts some genetic preservation. The robot arms of the machine pull unwound DNA strands through an aperture in its prow for examination after squeezing a DNA supercoil among its robot arms. In the meantime, the upper arms retrieve transcription factors from chains and then place them in intake valves. In comparison to the molecular structures of DNA and proteins, the information is stored in the database of a bigger nanocomputer located beyond the nucleus and attached to the cell-repair ship through a transmission connection. The DNA chain has the proteins reattached to it, the DNA chain re-twists into its initial shape having only a 50 nm diameter after the correction of any irregularities found in any structures. In comparison to most bacteria and viruses, the repair vessel might be smaller, but it would still be capable of delivering medicines (Adleman, 1995). Cancer, viral infections, and arteriosclerosis might all be destroyed if the sickness was attacked at the atomic level. Most human illnesses are caused by cellular molecular malfunctions, and cell activity is mostly regulated by protein production and gene expression. Increasing current genetical components by implanting fresh genetical components inside the nucleus is a standard procedure of gene therapy that has had limited success in humans but has shown promising results in animals. (Freitas, 2007).

Furthermore, due to immunological responses to viral carrier antigens, inflammatory reactions, insertional mutagenesis, and temporary efficacy, permanent gene substitution via viral couriers has mainly died in patients thus far. Leftover gene replicas, repetitive gene collections, incomplete trisomies, and higher polysomies can all lead to major diseases, which can sometimes be mistaken for ageing (Freitas, 2007).

Hematology: In the discipline of hematology, nanobots have the potential to be useful. Its applications in hematology vary from non-blood oxygen-carrying compound emergency infusions to immediate hemostasis restoration (Saadeh and Vyas, 2014).

An artificial red blood cell that can provide 236 times more oxygen than normal red blood cells is being developed by researchers at Stanford University in California, USA (Freitas, 2005a). There are three types of rotors in each respirocyte. While traveling through the body, one rotor releases the accumulated oxygen. All of the blood's carbon dioxide is gathered by the second

rotor, which then transports it to the lungs. Also, the third rotor extracts glucose from the bloodstream and utilizes it as an origin of energy (Mishra, 2012). This may be set up to remove carbon monoxide and other toxins from the body. A 5 cc medicinal dosage of 50% respirocyte saline solution includes 5 trillion nanorobots, enough to substitute the patient's whole 5.4 litres of blood in terms of gas-carrying capacity (Freitas, 2005b).

Microbivores, also known as nanorobotic phagocytes, are created as synthetic WBC. It is a diamond and sapphire information gadget with a 3.4-meter main axis diameter and a 2-meter minor axis diameter. Phagocytosis is the mechanism by which pathogens in the bloodstream are absorbed and digested by microbes (Eshaghian-Wilner, 2009). The prey bacterium links to the shell of the microbivores through a reversible binding site during the operational cycle. Internalized bacteria are put in a morcellation device and minced into nanoscale particles. A pre-programmed collection of digestive enzymes then processes and eject these microorganism bits (Manjunath, 2014). Microbivores work a thousand times quicker than antibiotic-assisted WBCs, and the pathogen has little risk of developing numerous medicine resistance, as happens with antibiotics. They can also be used to treat bacterial infections in the pulmonary and cerebrospinal systems, as well as infections in the urine and synovial fluids (Eshaghian-Wilner, 2009).

Clottocyte is an artificial platelet-like nanobot. Within 1 second, hemostasis would be complete. The reaction time is 100-1000 times faster than the normal hemostatic system, that takes two to five minutes to finish the overall procedure (Boonrong and Kaewkamnerdpong, 2011). Clottocytes have lowered the time it takes for blood to clot and the amount of blood that is lost. Blood clots are observed to form in some individuals on an irregular basis once again. Corticosteroids are used to treat this condition. However, they might cause adverse outcomes such as hormone production, lung damage, and allergic responses. Clottocytes can be employed as a non-toxic option in contrast therapy (Manjunath and Kishore, 2014).

Dentistry: Dentifrobots are nanorobots that are meant to be used in dental care (Abhilash, 2010). They are employed in hypersensitivity, orthodontics, cleaning, and tooth whitening(Sahoo et al., 2007).

Nanobot-enhanced mouthwash and toothpaste can detect as well as eradicate dangerous germs while preserving the mouth's natural flora. Food particles, plaque, and tartar may all be identified by these instruments, and they can be successfully removed. Nanobots replace both mineral and cellular components of dentition. Periodontal tissue which includes the periodontal ligament, alveolar bone, gingiva and cementum, can be manipulated by orthodontic nanobots (Sujatha et al., 2010). For infection therapy, Nanobots containing highly selective proteins that bind to pathogens of interest can be coated. In the event of a root canal, a small camera can be used to visualize the root and therefore eliminate any guesswork. The numeral and width of dentinal tubules in hypersensitive teeth are greatly enhanced, and nanobots with particular Obstruction or elimination abilities can inhibit these impulses in minutes (Sharples, 2011). In nano-dental procedures for comprehensive tooth restoration, a variety of tissue engineering techniques is utilised. In particular, comprehensive dentition replacement is achieved by fabricating and implanting a biologically endogenous whole replacement tooth that incorporates both mineral and cellular components (Wang, J. et al., 2011).

Nanodentistry has developed a sapphire-based nanostructured composite material that improves tooth durability and attractiveness. A synthetic substance with a covalent bond called sapphire is used to substitute the top enamel layers. This substance has 200 times the failure strength of ceramic and is 100–200 times tougher. Sapphire is quite vulnerable to acid corrosion, quite like enamel. Sapphire offers most outstanding bleaching gel, also available as a cosmetic. Nanocomposites are a new restorative nano-compound that increases resilience of teeth. Distinctive distinct nanoparticles that have been uniformly disseminated in resins or coatings and submicron are used to create nanocomposites. As a nanofiller, an aluminosilicate powder with an alumina to silica ratio of 1:4 and a mean particle size of around 80 nm is utilized. With a dispersion scale of 1.503, the nanofiller offers better toughness, elastic properties, radianc, esthetic attraction, excellent color intensity and gloss, and a 50% decrease in sealing shrinkage. They function better than conventional composites and blend in much better with remaining tooth structures.

Anti-HIV nanobots: HIV damages immune system, making the keeper weak to minor infections. AIDS becomes a lethal illness as a result of this procedure. WBCs are attacked by HIV, which converts them to HIV. As a result, the immune system collapses, resulting in the patient's death. This lethal illness has no known treatment. HIV-affected WBCs are converted to their normal state using nanobots, permitting the immune system to preserve a controlled status of protection (Bhuyan and Bardoloi, 2016).

Surgery: Surgery is an intensive procedure that might lead to complications. It is both a costly and tedious procedure, the success of which is dependent on the expertise and creativity of the operative surgeon and his team. Using nanobots, these constraints can be bypassed. (Eshaghian-Wilner, 2009) Inside the body, a surgically designed nanorobot can function as a partially automated onsite doctor (Kshirsagar et al., 2014). Inside the body, a surgically designed nanorobot can function as a partially automated onsite doctor. It would carry out a variety of tasks, including pathology identification, diagnosis, and lesion correction. All of this would be controlled by an onboard computer (Manjunath and Kishore, 2014).

Diabetes: The goal of the nanobots is to keep blood sugar levels at or below 130 mg/dl, which is considered a benchmark for blood glucose levels at a normal glucose concentration (BGLs). A removal scope of 30 mg/dl can be utilised and can be modified conditional on medications. Medical nanobots can be configured in a manner that the significant metric details is instantly communicated to the patient's mobile phone through radio frequency signals, and if the blood sugar level reaches crucial levels, the nanobots send an alert via the mobile phone (Abhilash, 2010).

Human sodium-glucose cotransporter type 3 (SGLT3) controls extracellular glucose concentrations and establishes blood glucose levels, as well as acting as a detector to detect glucose. Nanobots, according to Nandkishore et al., employ chemosensors that modulate SGLT3 glucosensor activity. Nanobots can successfully assess the need for insulin and other treatments with the assistance of this chemosensor (Kshirsagar et al., 2014).

Tetanus: The bacterium Clostridium tetani, which is normally found on the surface of rusted nails and metallic objects, causes tetanus. When a rusty nail or metallic item punctures a bodily surface, this bacteria may penetrate the body and produce the neurotoxic TeTx in a quickly. TeTx is a neurotoxin that causes paralysis of the entire body from head to toe, resulting in death. Anti-tetanus vaccination, which counteracts C. tetani and the neurotoxic TeTx in a short amount of time, is the standard therapy. However, it has many adverse consequences, including fever, redness, and severe swell surrounding the injection area. It can induce brachial neuritis in rare circumstances. A programmed nanobot can be used as an alternative therapy. When injected into the body, this nanorobot kills C. tetani and the fatal neurotoxin TeTx it releases, allowing the body to repair at a cellular level without the adverse consequences of traditional immunization (NAGAL et al., 2013).

Myocardial infarction: Nanobot molecules can identify and eliminate the blood canal obstructing components or plaque that causes myocardial infarction. Traditional therapy for myocardial infarction, such as angioplasty, is dependent on surgical abilities and can have adverse effects, but the nanobot procedure is resistant to these negative results (Biswas and Sen, 2014).

Gout: Gout is a disorder that occurs when the kidneys lose their capacity to eliminate waste from the bloodstream as a result of fat breakdown. This waste can occasionally solidify near joints, such as the knees and ankles, causing excruciating discomfort. The crystalline formations at the joints might be broken up by a nanobot, providing relief of symptoms (Strickland, 2010).

Alzheimer's disease: As a sign of Alzheimer's disease, amyloid protein deposits display alterations on gradients. This information aids in the earlier detection of Alzheimer's disease and the development of prospective immunotherapy therapies, such as more effective distribution of neurotransmitters like dopamine and amino acids like g-aminobutyrate (GABA) and more reasonable medical administration, such as nanorobots (Cavalcanti et al., 2007).

Damaged tissue repair: Existing molecules are replicated, and new molecules are assembled into new layers of tissue, that is how nanobots may readily repair and mend damaged tissue.

Nanorobots can regenerate broken bone fragments over time. It is believed that nanobots will be able to create bone marrow one day. Closing a broken vein, rebuilding damaged skin, and eliminating dead flesh from a wound are some of the further useful opportunities in the field of restoring injured tissues (Biswas and Sen, 2014).

Breaking up the kidney stones: Ultrasonic shocks can break up kidney stones using nanorobots. Kidney stones are uncomfortable, and do not pass through the urine. Doctors sometimes use ultrasonic frequency to break up these stones, although it is not always successful. Nanorobots uses a tiny laser to break up kidney stones, and the smaller bits are excreted in urine past the body (Martinac and Metelko, 2005).

Skin diseases: Skin problems may be treated with a lotion containing nanobots. It eliminates dead skin and excess oil, replenishes lost oils, applies the appropriate quantity of crude moisturizing substances, and aids in in-depth pore purification(Cavalcanti et al., 2004).

Anesthesia induction: Nanobots can be employed for both general and local anesthesia. It minimizes anesthesia-related morbidity and death by being very targeted and target-oriented (Agarwal, 2012).

Body surveillance: Nanobots allow for continuous monitoring of key organs and wireless transfer, which is not achievable with traditional drugs (Abeer, 2012). It will also respond quickly in the event of a rapid change in important organs or warn of potential concerns, such as excessive blood sugar level in the matter of diabetes (Bhat, 2014).

Nanorobots for detoxification: Autonomous nanorobots with great cleaning potential have also been employed as strong detoxification equipment. Detoxification techniques, like biosensing, depend on autonomus nanorobots to quickly absorb and terminate toxins from the environment, rendering them harmless.

If there were more efficient motion, toxins would clash and bind to the motors covered with the needed functional components. Nanomotors, for instance, have been mixed with crude compounds produced from cells that may mimic their parent cells' intrinsic characteristics to create unique nanoscale biodetoxification devices. Red blood cells (RBCs) have demonstrated an

exceptional capacity to act as a microsponges that absorbs toxins in circulation, neutralizing as well as removing "pore-forming toxins" (PFTs) (Hu et al., 2013).
Water-powered micromotors for detoxification could efficiently absorb and neutralize toxins in bodily fluids. RBC membranes could be used as a biomimetic platform for the efficient absorption and neutralization of PFTs (Wu et al., 2015b).

Nanobots for targeted delivery: Systemic circulation, as well as the control and navigation required for localized allocation and permeation of tissue, are essential for drug delivery nanobots. Drug delivery vehicles must have some distinctive characteristics, such as propelling power, controlled navigation, and tissue penetration, to ensure accurate delivery of medicinal shipments to selected infection areas. The motor-like nanobots can supply medicinal loads straight to infection locations, enhancing healing effectiveness while lowering systemic adverse consequences of very hazardous medications (Li et al., 2017). Some exploratory tests have been carried out in test tubes and in vitro to verify the shipment effectiveness also the execution of these nanorobots. Wu et al., 2015a, for example, created a multilayer tubular polymeric nanomotor with a porous membrane template and enclosed it in doxorubicin, an anticancer medication. That nanomotor delivered the drug to cancer cells successfully (Wu et al., 2013). When compared to passive targeting without propulsion, Ma and others in year 2015 revealed a chemically driven Janus nanomotor that served as an effective microscopic payload distribution device with 100% penetration enhancement (Ma et al., 2015). Compared to their static nanowire counterparts, SiRNA-loaded nanowires were conducted to diffuse quickly within several cellular lines, considerably improving gene silencing efficacy and speed. There were also magnetized helical microswimmers utilized to transfer plasmid DNA (pDNA) to human embryonic kidney cells. When the pDNA-loaded motors came into touch with the cells, they discharged their hereditary payload inside the cells (Qiu et al., 2015).

Studies of in vivo activities of nanobots: Although preliminary in vivo researches have previously been conducted and show promising outcomes, the majority of the study has been done in vitro. The first in vivo study of chemically driven micromotors was just completed by (Gao et al., 2015). Stomach acid production has improved the bonding and holding of micromotors, or motors, in a mouse's digestive tract. The motors slowly disintegrate in stomach

acid, discharging their loads and ditching no hazard back(Gao et al., 2015). Nanorobots that attack tumour cells by cutting off their blood supply were tested on mice and pigs. Mice with melanoma,breast cancer, lung cancer and ovarian cancer, had the nanorobots administered intravenously into their bloodstream. Within hours, the nanorobots had discovered and enveloped the tumours. Tissue injury caused by a blood supply blockage was evident within 24 hours. After 48 hours, developed blood clotting was noticed, and after 72 hours, blood clots were observed throughout the tumor. Nanobots were definitely effective in destroying malignant cells, but the consequences would be far worse if they were able to assault healthy tissue. But, thankfully, such an incident did not occur. Nanobots were also administered to tumor-free mice and pigs, but no changes in blood coagulation or cell shape were observed. The efficacy of nanobot therapy against some tumours provides tremendous optimism for the future (Murnane, 2018). The nanobots can be expelled from the body in two ways. Once their tasks are accomplished, nanobots may be expelled from the body through human excretory pathways. Active scavenger systems can also be used to eliminate them (Requicha, 2003). Secondly, cleaned blood could be transferred from the patient to a specialist centrifugation device. Auditory transmitters instruct nanorobots to achieve unbiased stability. Because nothing else in the blood that is solid may retain complete unbiased stability during moderate centrifugation, they precipitate outward and are reintroduced back into purified plasma on the opposit side of the device. Conversely, following centrifugation, the plasma containing largely stopped nanobots but occasional other solids is sucked off via a 1micron filter, eliminating the nanobots. Sorted plasma is blended solid components that have been centrifuged and safely reintroduced back into physique of the patient (Kharwade et al., 2013).

Chapter 7

Advantages And Limitation

7.1Advantages of nanomedicine:

- It increases bioavailability.
- It is used for targeted drug delivery instances as just cancerous cell treatment.
- Less errors due to robotics and control via computers.
- Reaches distant regions of the various body parts which are non operable on the operating table for a surgeon.
- Compounds being delivered by nanorobots during molecular diffusion, allowing for such benefits of a large surface areas to be achieved.
- Non-invasive method.
- Nobs on the computer regulate the quantity, recurrence and releasing duration
- Improved accurateness.
- In locations where treatment is not needed the medication is ineffective. Which minimizes unfavourable side effects (Khulbe P, 2014).

7.1 Limitations of nanorobot

Although nanomedicine has a wide range of uses and many advantages, it is not perfect. Because, when the shift from micro to nanoparticles starts, the size range narrows significantly and the number of surfactant molecules rises. Significant issues like sticking and inter-particular friction arise as the surface area increases. Additionally, due to their tiny size and very high bodily clearance rates, nanoparticles may not be suitable for use in medication administration or diagnostics (Rahul, 2020). A material that isn't hazardous at 100 nm can turn hazardous at 1 nm or vice versa, causing a variety of physical and chemical interactions. Chemical composition, exterior layout, exterior charge, solubility, and the presence of functional groups are additional variables that may affect toxicity. It is also a matter of concern how the particles will act inside the body under different conditions and if they can infilter the cell membrane. Because of the enhanced chemical reactivity of nanoparticles, reactive oxygen species (ROS) are produced, which can induce oxidative tension, inflammation, and damage to DNA, proteins, and membranes, eventually guiding to toxic effect also it potentially lead to neurological conditions like Parkinson's and Alzheimer's disease (Shubhika, 2012). These particles may interact in unexpected ways inside the body, which might result in unanticipated outcomes. Additionally, they may act independently of the body while inside it, entering capillaries, moving from the area of injection to different body areas, spanning cell surface, and perhaps breaching the

blood-brain barrier (Rahul, 2020). Since they can pass the blood-brain barrier, nanoparticles are an excellent means of delivering medications directly to the brain. On the other hand, this is also a significant disadvantage since drug-carrying nanoparticles may be harmful to the brain.

Research conducted in vitro on recently created nanotubes revealed that they may result in changes in cell shape as well as ROS generation, oxidative stress, lipid peroxidation, and mitochondrial malfunction. They could cause platelets to aggregate. High dosages of their intratracheal installation may cause lung damage and persistent lung inflammation. Additionally, these carbon nanotubes may clog the airways, reducing the lungs' ability to absorb oxygen (Shubhika, 2012).

Studies have shown that nanoparticles may build up in many animal organs. In addition, we are unable to foresee whether the organisms will be able to eliminate them or if they would collect within the body. While biodegradable nanoparticles are often expelled, non-biodegradable ones might injure body parts by accumulating there (Shubhika, 2012).

In addition to the apparent concerns to the patient, nanomaterials may also be harmful to the ecosystem and may need to be processed before being disposed of. The non-biodegradable ones run the risk of contaminating the soil, the water, or the air. It is difficult to foresee how they may affect the environment, and it is unknown if they will destroy the biome. It would be very difficult to eradicate them if they were to penetrate the bio-network through the plants. The expensive cost of employing nanotech in medication is another drawback. The adoption of nanomedicine would raise the expense of healthcare, making it more difficult for the poor to receive it (Shubhika, 2012).

Chapter 8

8.1Conclusion:

Nanobots, an innovation in the field of nanotechnology, provide promise for the detection and remedy of a variety of dangerous diseases such as heart disease, cancer, genetic disorders, HIV,

and diabetes with few adverse consequences. It's also incredibly valuable in the fields of dentistry and surgery. In comparison to current medication delivery systems, nanorobots have a lot of benefits. A few good examples include improved precision, less side effects, enhanced bioavailability, targeted therapy, reduced surgical errors, access to remote areas of the human anatomy, large interfacial areas for mass transfer, non-invasive methods, computer control of distribution, non-invasive methods, and faster drug action. Sensitive new diagnostics will be applied in healthcare in the future to enhance individualized risk analysis. The greatest benefit may be predicted if the following main disorders are addressed first: diseases of the heart, cancer, the musculoskeletal system, the nervous and mental systems, diabetes, and viral infections. Nanomedicine has the potential to improve treatment and early diagnosis, and enhanced follow-up care, making medical care more inexpensive and efficient. Nanomedicine will also enable better-personalized therapy for several illnesses by using a deep understanding of diseases at the molecular level.

Scientists believe that during the next ten years, our blood will be overflowing with microscopic nanobots that will aid in keeping people healthy. These will function at the molecular level, safeguarding the biological system and promoting healthy and prolonged life.

More research should be conducted on nanorobots to improve the design and functions of nanobots, as well as their efficacy and safety in the human body.

8.2 Future perspective:

Xenobiotics are "programmable living robots" constructed from live, organic tissue. They have been made in a variety of simple forms, some of which include legs. The future of xenobiotics is uncertain due to ethical concerns, but they could benefit human, animal, and environmental health. scientists working in this field are enthusiastic about their potential applications in removing microplastics from the ocean, removing toxins and radioactive materials from hazardous locations, improving the efficiency and effectiveness of targeted drug delivery, and repairing cells and tissues (Moore and Sarah, 2021).

Also, The collective actions of nanobots that resemble those in nature are known as "nanobot swarms." A group of scientists used a mouse model to study the nanoparticles' migration by injecting it into mice and monitoring the resulting fluid movements. According to the results, they may be accommodating in a viscous medium, enabling more precise medication delivery (Moore and Sarah, 2021).

Scientists are thinking that Real-time data extraction and brain-state monitoring might be made possible by using nanobots to wirelessly send information stored in the brain to a supercomputer network in the cloud. However, extensive research and design work as well as overcoming the ethical and moral ramifications must be done before this use of nanotechnology can become a reality (Moore and Sarah, 2021).

There has been much study, but much more will be required to build a functioning nanobot capable of doing activities helpful to humans; surface alterations, structures, components, and physiological reactions must all be thoroughly understood. However, rapid advancements in nanotechnology, biotechnology, and computing science will impact the rapid development of nanobots. Researchers are currently in the design and experimenting stages at the moment (Vega Baudrit, 2017).

Table 1: Micro and nanorobotic research is moving towards the clinic (Zamecnik, 2022)

Product Name	**Company / Institution**	**Application**	**Development Stage**
Stem Cell Navigator	Biot Korea Inc	Drug Delivery	Pre-Clinical
Next Generation Nanorobotic System	University of Hong Kong	Cancer Therapy	Early development
Nanorobot Device	Indian Institute of Science	Dental Procedures	Pre-Clinical
Nanorobot Based Insulin Pumping Device	Pennsylvania State University	Diabetes Management	Early development
Nanorobot Based Drug Delivery System	Pennsylvania State University	Drug Delivery	Early development
Molecular Nanomachine	Nanorobotics Ltd	Drug Delivery	Pre-Clinical
Microrobot	University of Science and Technology of China	Drug Delivery	Pre-Clinical
Microrobot	ETH Zurich Foundation	Drug Delivery	Early development
Microrobot	ArteDrone SAS	Surgery	Early development
Microrobot	Ecole Polytechnique Federale de Lausanne	Drug Delivery	Early development
Micro-Scale Tumbling Microrobot	Purdue University	Drug Delivery	Pre-Clinical

MEMS Device	Elbe Valley Medical Ltd	Cancer Therapy	Early development
FMSMs	The Chinese University of Hong Kong	Diagnosis Of Clostridium Difficile Infection	Clinical (in stool samples)

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