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# Enhancing Oncology with Nanorobotics

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## Abstract
Lung cancer was ranked 6th among 'the top 10 global causes of death in 2019' by the World Health Organisation (WHO), with breast cancer and cervical cancer being the most common among Indian Women. The 2020 cancer death toll is devastating - approximately 10 million worldwide, with 8.5 hundred thousand in India. Common cancer therapies have a high failure rate because of various drawbacks - inefficient drug delivery, destruction of healthy cells around the tumor, and drug toxicity to name a few. The key attributes of efficient cancer management are - early-stage diagnosis and targeted therapy. Although nanomedicine has already been contributing to mitigate the drawbacks, advances in nanorobotics show that engineered nanorobots can be used to provide precision and expedition in early detection, and targeted drug delivery, ergo destruction of only cancer cells, leaving the normal cells alone. These computer-controlled nanomachines can be injected into symptomatic patients to perform diagnosis and therapy at a molecular level by sensing and destroying the cancer cells, and once their job is done, they would leave the body via excretory or respiratory systems. This would also minimize surgeon-patient contact. The application of nanorobotics in cancer theranostics, simultaneously performing diagnosis and therapy, holds a promising and revolutionized future of healthcare with an improved cancer survival rate. This review aims to outline the design, mechanism, applications in cancer diagnosis and therapy, and future outlook of nanorobots.

**Keywords:** Nanorobotics, Nanorobots, Cancer Therapy, Cancer Diagnosis, Propulsion

## 1.Introduction
Although the term 'nanotechnology' was coined late in 1974, by Norio Taniguchi [46], the birth of its concept dates back to the year 1867, when James Clerk Maxwell proposed Maxwell's demon, a thought experiment, in which a submicroscopic entity could handle individual atoms and molecules [44]. Later in 1959, in his lecture 'There's Plenty of Room at The Bottom', Richard Feynman introduced his friend and doctoral student Albert Hibbs' idea of the possibility for a relatively small machine to act as a mechanical surgeon, by putting it into the blood vessel, and this way one could "swallow the surgeon" [57]. In 2016, Jean-Pierre Sauvage, Sir J. Fraser Stoddart, and Bernard L. Feringa jointly received The Nobel Prize in Chemistry "for the design and synthesis of molecular machines". They had developed molecules with controllable movements, which could perform a task when energy was added [50].

Nanorobotics is the engineering of nanorobots - devices ranging in size from 0.1 to 10μm, made up of nanoscale or molecular components [78]. These nanorobots work at the molecular level and have high positional accuracy by navigation network [24]. Due to their size, much smaller than human tissues, they can easily traverse through the human body as bloodborne devices and can be of great benefit for medicinal purposes [60][65][4].

The normal cell cycle involves cell growth and cell division to form new cells when the body requires them, and once the cells get old or damaged, they die. Cancer is a medical condition that arises when the normal

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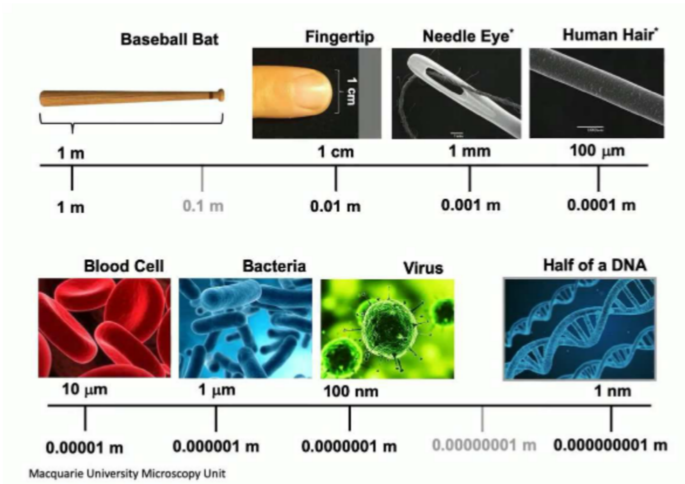


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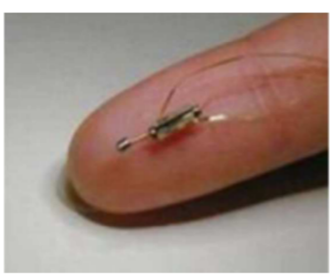
**Fig 1**. Comparative study of sizes of various objects in metre scale [45].

cell cycle is broken due to uncontrolled growth and multiplication of abnormal or damaged cells, which then invade or spread to other body parts as malignant tumors via metastasis. Cancer is one of the leading global causes of death [27]. Conventional therapies involve radiation, chemotherapy, surgery, which leave severe side effects within the patient's body and also have a high treatment failure rate due to late diagnosis [76][35], multidrug resistance [62][58][23][76], and instability of anticancer drugs, made of biological agents, *in vivo* circulation as they degrade and inactivate before reaching the target cell [30][71][74]. Nanotechnology offers to combat these drawbacks by providing diagnosis at cellular levels, encapsulating the anticancer drug into nanocarriers, and targeted drug delivery sparing the normal cells [47]. Once introduced into the bloodstream, these nanorobots would navigate and reach the target tumor, selectively releasing the cell-destroying agents to the cancer cells only, causing no harm to the non-cancerous cells. This would also allow the usage of lower doses of drugs [8]. Disease-specific receptors on cell surfaces provide useful targets for nanoparticles to recognize the disease at the cellular level and deliver therapeutic compounds [78][13].



Courtesy - The Scientist.

**Fig 2**. Picture of a nanorobot for checking blood contents [40][38].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Nanodiagnostic devices can provide early detection of severe diseases including several types of cancer as it allows the identification of disease at molecular levels even before the emergence of specific symptoms [43]. Nanorobots with embedded chemical biosensors can help in detecting tumor cells even at the early stages of development within the body [11][55]. For example, integrated nanosensors can be utilised in finding the intensity of E-cadherin signals [20][65]. Autonomous nanodevices, capable of drug encapsulation and targeted delivery, allow computer-controlled on-demand *in vivo* release of drugs with high loading rates, expedition, and precise targeting [37][43]. Nanorobots could purposely deliver drug molecules to one cell, but not to an adjacent cell, in the same tissue. R. A. Freitas named such drug delivery vehicles as 'Pharmacytes' [51][24]. These self-powered, computer-controlled, nanorobots are capable of precise transport, timing, and targeted delivery of pharmaceutical agents to specific cellular and intracellular target sites within the human body [54]. The discovery of this cutting-edge technology is of great benefit in the field of medicine, particularly for more precise diagnosis and efficient therapeutics that will improve the quality of life [78]. Their durability, faster functionality, capacity of self-replication to replace worn-out units, and targeted drug delivery directly are extremely advantageous for cancer treatment [42]. However, their development imposes quite a few challenges that need more research such as drug loading capacity and drug delivery at the subcellular level, biocompatibility (since different artificial materials will be introduced into the body) [14][43], and susceptibility to electrical interference such as radiofrequency and electromagnetic pulses generated by external sources [15]. Current advances in research focus on improving the manufacturing of complex molecular machines to achieve high assessment and precision at the cellular and molecular levels [42].

## 2. Design and Working

The body of the nanorobots is constructed using carbon in the form of diamond/fullerene nanocomposites (like carbon nanotube) due to their inert properties and strength. To avoid rejection from the host immune system, the outside surface of the nanostructures is covered with a passive diamond layer [10][42] and is made super-smooth [65]. The basic structures of a nanorobot include power source, sensors, actuators, onboard computers, pumps, and structural support. For biomedical purposes, the nanobot would contain additional substructures like a payload compartment that would carry the drug, a miniature camera for navigation, microwave emitters and ultrasonic signal generators that can kill cancer cells without disrupting the cell membrane, and also destroy arterial plaque, blood clots, and chemotactic sensors to detect and discriminate between different cell types by specifically recognizing their surface antigens [42]. Ultrasonic sensors around the body would avoid collision with other nanorobots and also with cells in the blood vessels [65].

### Control and Navigation

Depending on the application, acoustic, light, radiofrequency, and chemical signals may be considered as possible options for communication and data transmission of nanorobots [3][65].

Internally powered nanorobots can be communicated with the help of chemical sensors that would precisely guide them to the right location by detecting and following the track of specific chemicals released by the surrounding tissues. Once the nanobot reaches the target area, a spectroscopic sensor can be used to collect and analyse samples of the surrounding tissue. Externally driven nanorobots can be guided to the target site by an operator through the detection of ultrasonic waves and generated magnetic field (magnetic resonance imaging tracking), or by using radio waves, microwaves, X-rays, or heat. Alternatively, for efficient navigation, nano cameras can be fitted onto the nanorobots to render the live movement of the device to a monitor [42].



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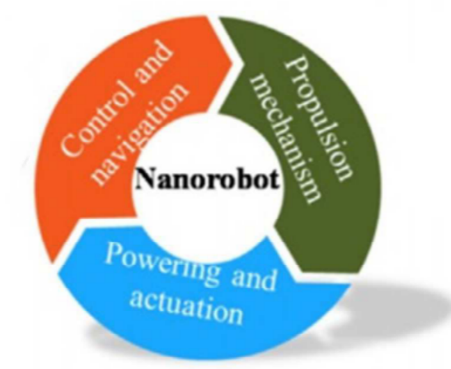




**Fig 3**. Main design features of nanorobots [42].

## Propulsion Mechanism

Considering their purpose to navigate through narrow channels of only a few hundred nanometers in diameter, the design strategy of propulsion mechanism of these nanorobots should take into account impediments such as low Reynolds number viscous drag and Brownian motion [10][8][29][42][43][5]. Based on their propulsion mechanism, the nanorobotic system can be categorized accordingly.

### Chemical propulsion

Chemical propulsion works on the principle of generating energy from localized catalytic reactions, which in turn is converted into a mechanical motion for the propulsion of the nanorobots [42]. Propulsion in aqueous media is achieved through gas bubbles or a local electric potential gradient generated from surface reactions [29]. The first nanorobot driven via chemical reaction was a spherical microparticle coated with Pt for catalyzing the decomposition of hydrogen peroxide $H_2O_2$ and generating $O_2$ bubbles [43]. PtAu and NiAu bimetal nanorods generate current via this mechanism [42].

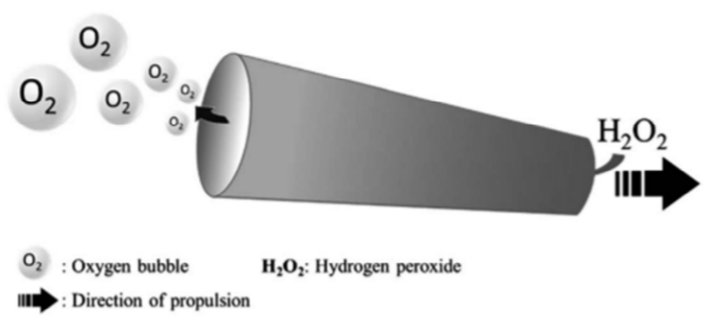




Fig 4. Schematic representation of bubble propulsion mechanism. The inner surface is coated with Pt to catalyze $H_2O_2$ decomposition generating $O_2$ bubbles for propulsion [36].


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This propulsion mechanism has few drawbacks such as reduced ability to penetrate tissues and cellular membrane and toxicity of the solvents [43]. For better precision, and to avoid using chemical fuel, various other mechanisms are an alternative [36][42].

**Physical propulsion**

Propulsion via magnetism is inspired by the motions of the natural swimming organism with helical flagella and can be controlled remotely or wirelessly. This mechanism works on the theory that a uniform external magnetic field, when applied to a magnetic object, has the ability to rotate the object till it becomes aligned with the magnetic field, but while the rotation axis of the magnetic field is being modulated, the object can be moved in different directions. The first microscale magnetic helical robot, with a diameter of 3 mm and a length of approximately 30-40 nm, was developed in 2007 in Zurich, while the first nanoscale prototype with magnetic propulsion was developed two years later in 2009. This concept was initially anticipated as a microrobot with a magnetic head and helical tail, and was named “artificial bacterial flagellum” [18][43].

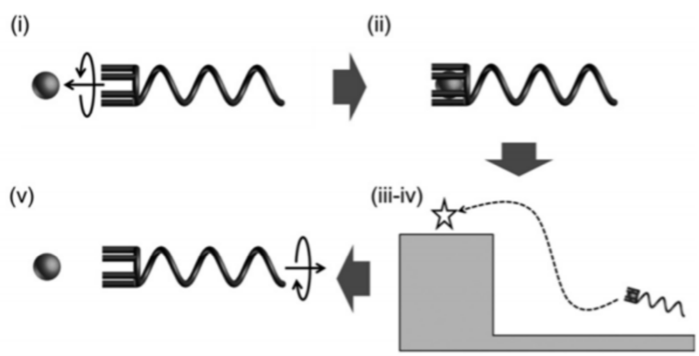




**Fig 5**. Illustration of transportation of colloidal microparticles, using individual helical micromachines with a microholder fabricated together with the helical body, in four stages - (i) approaching, (ii) loading, (iii-iv) transporting in 2-D and 3-D, and (v) releasing [67].

A more attractive approach to nanorobot propulsion, considering their application in the biomedical field, would be via ultrasound. This would also help in drug delivery to the brain as it would be able to bypass the blood-brain barrier [37]. Reportedly, ultrasound-controlled nanoporous gold-based nanomotors were developed for targeted drug delivery and could trigger drug release around a cancer cell [70].

Light-driven propulsions are of advantage as incident light can be used by itself without the need for supplementary energy sources, such as chemical reactions. This is based on various mechanisms like (i) electrophoresis/electrolyte diffusiophoresis where the Coulomb interaction is the dominanting force between the charged surface of the nanodevice and oppositely charged Debye layer, (ii) In the case of non-electrolyte diffusiophoresis, the dominant force is represented by van der Waals, dipole, or hard-sphere interactions, limited only to a few molecule layers. By adjusting the light intensity, speed can be precisely controlled. Isotropic structures can be used in the designing of the nanorobots to provide them movement without being influenced by their Brownian diffusion, but just to follow the irradiated light direction [16][43].

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**Biological propulsion**

The biological propulsion of nanorobots involves the conversion of chemical energy into kinetic energy by protein nanomotors that move in a revolution, linear motion, or rotate. Proteins, DNA, and carbon nanotubes can act as power sources, structural links or biosensors of a nanorobot for medical applications. Biologically propelled nanorobots can be self-replicated. They have high efficiency and high molecular recognition specificity. DNA packaging nanomotor found in the *Bacillus virus phi29* is reported to be one of the most powerful nanomotors [42].

Based on the conversion of ion-motive force into mechanical force, intact flagellated bacteria cells are used as propellers in bacterial propulsion mechanism. For example, *Escherichia coli* for drug-loaded microparticles [66][43]. Additionally, the flagellum may also act as a sensor detecting changes in chemical concentration and temperatures in the surrounding [42]. Because of the pathogenicity of bacteria in humans, this propulsion mechanism is not very attractive for medical purposes [43].

Sánchez et al. developed *Escherichia coli (E. coli*) biohybrid microswimmers. *E. coli* were incubated with 2 μm diameter metal-capped (Pt, Fe, Ti, or Au) polystyrene Janus particles [39]. Janus particles are micro/nanoparticles, the surface of which have two or more different physical properties, that can have at least two different types of chemistry\on the same particle [22][31]. The motion was propelled via the bacterial flagella [43].

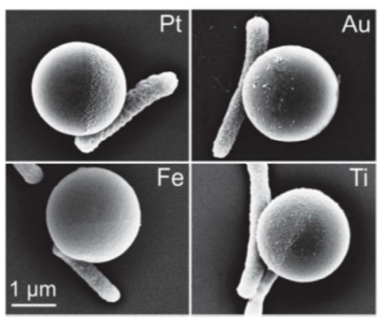





**Fig 6**. Scanning electron microscope (SEM) images of *Escherichia coli* attached to metal-capped (Pt, Au, Fe, Ti) Janus particle [39].

## Powering and Actuation

Internal powering of nanorobots relies on its inbuilt propulsion system generated by energy-rich molecules, such as glucose and oxygen [68], through multiple chemical reactions or piezoelectric materials, such as zinc oxide nanowires [77].

External powering is done via different sources, such as magnetic fields, ultrasound waves, infrared and radiofrequency radiation. [15][59][32][42]. Radiofrequency-based telemetry procedures have demonstrated good results in power transmission with the use of inductive coupling. The energy can also be saved in ranges of ~1 μW while the nanorobot stays inactive, becoming active only when signaled to [65].

Another approach in designing internal powering navigation makes systems makes use of biological macromolecules capable of undergoing conformational transformations in response to various stimuli

DNA motors) [28][75], which derives energy from the hydrolysis of biomolecules such as adenosine triphosphate (ATP) [42].

## Application of Nanorobots in Cancer Diagnosis

Nanorobots can be inserted into the body to identify tumor cells [51][44]. Embedded chemical biosensors on their surface can help detect variations in the surrounding environment's status [42].
Various nanoparticles useful for diagnostic purposes include [2]:

**Nanoscale cantilever** coated with antibodies to which proteins secreted by cancer cells bind specifically, causing a change in its physical properties and thereby detecting the disease [2].

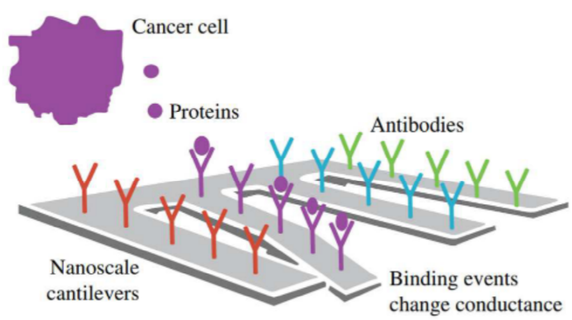


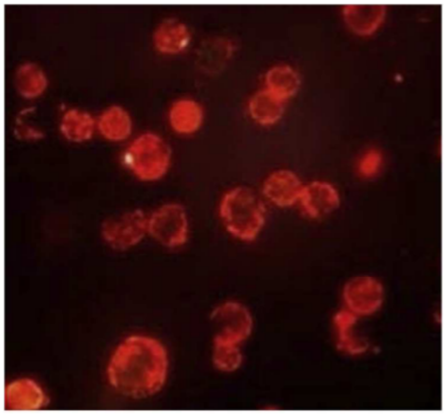



Fig 7. Schematic representation of detection of cancer cells by nanoscale cantilevers [2].

**Carbon nanotubes** as they can act as DNA biosensors. They search for covalently bonded DNA oligonucleotides, and when hybridization between the probe and target sequence occurs, the voltammetric peak picks up that change [61].

**Quantum Dots** linked to antibodies that would create arrays capable of detecting multiple substances simultaneously. Their photochemical stability and the ability to tune broad wavelengths, make them extremely useful for bio-labelling purposes [48].

**Gold Nanoparticles** as they readily get conjugated to antibodies and other proteins due to the affinity of functional group thiol (-SH) for their gold surface. In addition to spherical gold nanoparticles, gold nanoshells and nanorods have also been applied for biomarker detection purposes [9][41][73].
An example of a nanodetection system is a nanomotor with the ability to sense intracellular endogenous miRNA, designed for the detection of breast cancer cell line MCF-7 and cervical cancer cell line HeLa, based on graphene oxide (GO) coated gold nanowires (AuNWs) functionalized with a dye-labeled single-stranded DNA (ssDNA) chain. This detection is based on real-time monitoring of possible miRNA-21



Courtesy - Ocean NanoTech

**Fig 8.** Breast cancer cell line SK-BR-3 after exposure to Quantum dots [79].

expression within the above-mentioned cells by ultrasound-propelled nanorobots. Once they have penetrated the intact cancer cells, the dye is released, showing fluorescence. Then depending on the presence or absence of the target miRNA, the nanorobot obtains an "on/off" sensor, [12]. These nanorobots can assess the differential endogenous expression of a target miRNA in single intact cells within a few minutes and are hence more advantageous over other existing miRNA detection methods which are more time consuming and require greater number of cells [72][43].

## Application of Nanorobots in Cancer Therapy

The nanoscale-engineered robots have unique properties such as increased surface area, charge, reactivity, and other physicochemical properties, which do not exist in other larger-scale medical devices [42]. The motion of cellular drug carriers towards tissues is random and difficult to control, therefore the autonomous displacement capacity of nanorobots recommends their use in facilitating targeted transport of the substances administered in severe diseases, including cancer. [43][72]

Depending on the application area, R. A. Freitas classified these nanorobots as respirocytes, microbivores, clottocytes, pharmacytes, dentifrobots, chromallocytes, etc. [42][51] of which pharmacytes are drug-delivery vehicles capable of carrying up to 1 $\mu m^3$ of payload drug stored in onboard tanks [34], which can be discharged into the immediate extracellular fluid or transported directly into the cytosol using a transmembrane injector mechanism [52][53]. They are used for delivering drugs, controlling the cell signals, or/and modifying the intracellular message with a preprogrammed one [42][54]. Once their task is completed, these pharmacytes can be recovered from the patient via apheresis or excretory pathways [52][54]. Minimally invasive targeted therapy can be achieved through wireless manipulation and positioning of drug delivery systems (DDS) [49]. Nanorobots are injected into the bloodstream in one dose with the target of seeking and destroying the cancer cells sparing healthy ones [1]. Drug-loaded nanoparticles can be applied for therapy, where the therapeutic agents would adhere to the cancer cell, with the help of RNA strands located on the surface of nanoparticles, and then release the drug locally [33]. Lipid-like molecules, assembled as nanocapsules, conducted the RNA molecules to the cell cytoplasm [42].



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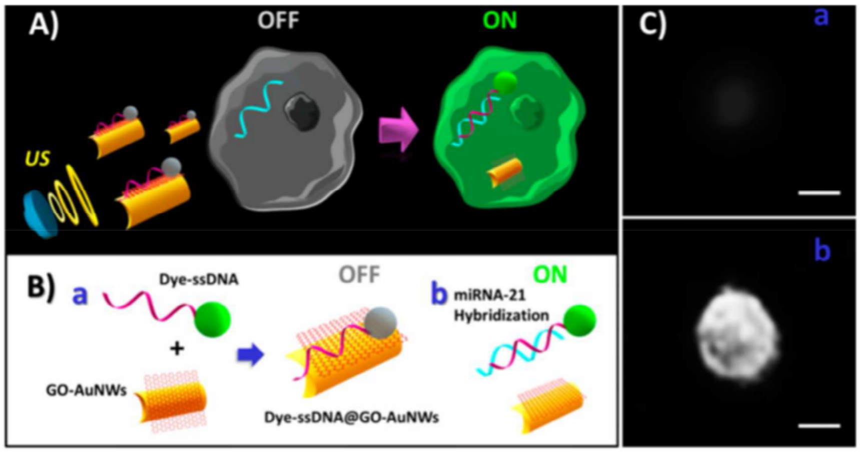




**Fig 9.** Schematic illustrations of (A) the "OFF-ON" fluorescent sensing to specifically detect miRNA-21 in intact cancer cells, and (B) steps involved: (a) deactivation of the dye-ssDNA on the GO-functionalized AuNWs and suppressing of the dye fluorescence, and (b) fluorescence recovery due to release of the dye-ssDNA from the motor GO-quenching surface upon hybridization with the target miRNA. (C) Fluorescence images of an MCF-7 cell (a) before and (b) after 20 minutes incubation with the ssDNA@GO-modified AuNWs under an Ultrasound field (with 6 V and 2.66 MHz). Scale bar, 10 µm [12].

Various materials that can be utilized as nanocarriers for the encapsulation, transport, and release of therapeutic drugs include [65]:

**Dendrimers** as a single dendrimer has the ability to carry a molecule for recognizing cancer cells, another for destroying those cells, and one that would detect the signal of death [69].

**Nanoshells** with bioactive substances that would specifically bind them to cancer cells [2]. They have a silica core and the outer layer is metallic, the thickness of which can be manipulated to design beads to absorb near infra-red light, which would create an intense heat lethal to cancer cells [69].

**Liposomes** due to their easy preparation, acceptable toxicity, and biodegradability profiles. The drug can be loaded via liposome formation in an aqueous solution saturated with soluble drug [19].

**Polymeric Nanoparticles** which include nanospheres and nanocapsules. They can absorb, dissolve, encapsulate, or covalently link therapeutic drugs to the polymer backbone through a simple ester or amide bond that can be *in vivo* hydrolyzed through a change of pH. These are solid nanoscale carriers, made of natural or artificial polymers, which are generally biodegradable. They are limited by poor pharmacokinetic properties like the uptake by the reticuloendothelial system (RES) [7].

**Polymeric Micelles** as their hydrophobic core can carry lipophilic drugs by solubilizing and physically entrapping within the core. These have high loading capacity and are biodegradable spherical nano-carriers that can co-deliver two or more therapeutic substances, simultaneously. The drug is released by eroding the biodegradable polymers or diffusing through the polymer matrix [17].

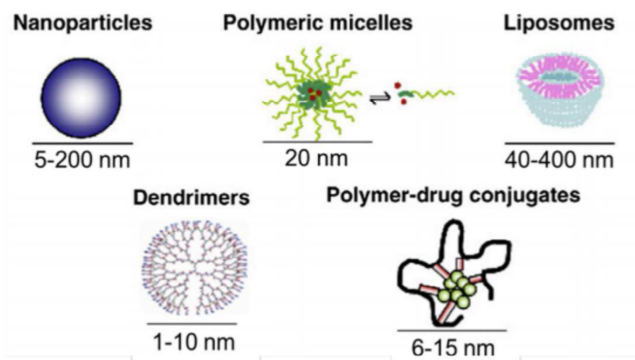




**Fig 10**. Illustration of various nanocarriers in current cinicical studies [21].

Nanocarriers as DDS (5-200 nm) have been thoroughly explored for therapy, with many already being approved by the Food and Drug Administration (FDA) to treat neurovascular diseases, neurological cancers, and neurodegenerative maladies [26]. It was demonstrated that anticancer drugs with aromatic structure, like doxorubicin (DOX), can be loaded directly on the carbon-based DDS via adsorption, with loading efficiencies up to 200% being reported for this compound [43].

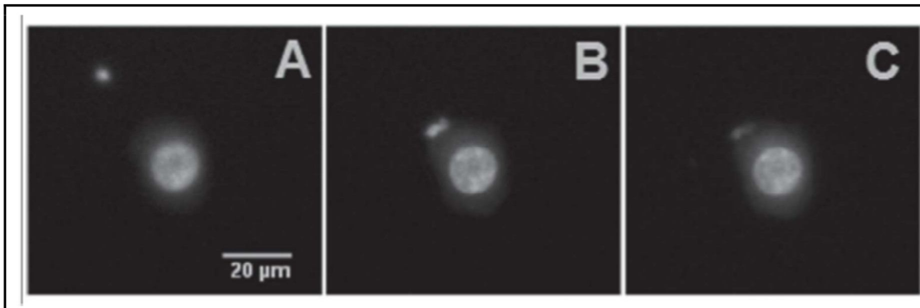




**Fig 11**. Time-lapse fluorescent images of ultrasound propelled (6V and 2.01MHz) DOX-loaded nanoporous Au nanomotor - A: travelling towards a HeLa cell, B: approaching the HeLa cell, and of C: the nanomotor and the HeLa cell after 15 minutes of NIR irradiation [70].

Although this method eradicates the need of additional functional groups, the water solubility of these carriers, and their toxicity, are areas that still need more development. The performance of bismuth/nickel/platinum-based multilayers tubular microrobots was tested for the same drug, DOX, and owing to its biocompatibility, bismuth was chosen to cover the microrobots [43].
Recent development towards the DNA nanotechnology domain is the use of DNA origami as structural components for the construction of nanoscale machines by exploiting the specific interactions between complementary DNA bases. The DNA nanorobots are rigid constructions with sizes between 10 to 100 nm [43]. They look like a nanoscale open-ended barrel with two halves connected by molecular hinges. Molecular payloads can be hosted within the cavity, secured by molecular anchors, and aptamers (short nucleotide strands with special sequences for recognizing molecules on the target cell) attached on the outside. These nanorobots exist in on and off conformations - tightly closed in off position, bypassing the normal cells, and on recognizing the target cell, in the on position, the two halves open up and deliver the drug payload to that cell [56].
Reportedly, DNA-based nanorobots have been developed to triggercoagulation within the blood vessels of tumors, causing destruction to the cancer cells through starvation [25]. A tube-shaped DNA nanorobot (19 to 90 nm), made using DNA origami technique, was tailored to deliver thrombin, positioned within its cavity, specifically into tumor vessels to induce thrombosis for tumor therapy. When applied to tumor-bearing mouse models, the exposed thrombin activated localized coagulation to selectively block tumor blood vessels, thereby destroying the tumor [64][43]. DNA nanorobots are able to identify 12 types of cancer cells [42][56].

## Challenges

Nanorobotics in medical application is a relatively newer field and has quite a few challenges that need to be worked on, before bringing the nanorobots to routine clinical use. It is expensive to design the nanorobots, and many complications are involved in designing them.
Nanomaterials have large surface area - volume ratio, and are hence more reactive, and have a high rate of absorption through various organs. Thus, after prolonged use, these have high chances of getting accumulated in different organs. For example, they may cause inflammation of the alveoli in the lungs and subsequent cell damage. [24]. The biocompatibility and degradation pathway of materials used require special attention [43]. Susceptibility of electrical nanorobots to electrical interference, such as radiofrequency and electromagnetic pulses generated by external sources, is also a limitation [15][42].
Another challenge is to overcome the high viscosity of the fluid at low Reynolds numbers for better efficiency, which can be achieved by the integration of catalytic nano-materials and processes to decompose chemical fuels. However, up to the present, hydrogen peroxide has been employed as a fuel which has limitations due to its toxicity especially for potential applications in biomedicine, and hence there are high demands on finding more biocompatible fuels. [43].

## Conclusion

In 2012, scientists at the Wyss Institute, Harvard University loaded fluorescent-labeled antibodies against human leukocyte antigens into the nanorobots to make them bind specifically to the cancer cells. Once the target proteins were detected, the nanorobots would release the payload [56]. In 2017, scientists at the California Institute of Technology developed a nanorobot out of a single strand of DNA that could pick up and drop molecules at designated sites [6]. In 2018, scientists at the Indian Institute of Science, Bangalore designed mobile nanotweezers by combining plasmonic tweezers with magnetically helical nanorobots. These nanotweezers can trap objects at the nanoscale and reach target objects with control to capture, transport, and release cargo with expedition [63].


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When applied for diagnosis and therapy purposes, nanorobots can provide precise imaging and controlled targeted drug delivery. DNA nanorobots can recognize 12 types of cancer cells. These can also be used, with further research and improvements, to prevent hereditary cancers. As mentioned in the abstract, breast cancer and cervical cancer are the most common types of cancer found among Indian women. Nanorobots can help in the early detection of these diseases, and hence would improve the chances of successful therapy. These would also reduce the surgeon-patient contact.
However, lots of improvements and clinical trials are needed before putting these to medical usage. Current advances in research focus on improving the manufacturing of complex molecular machines to achieve high assessment and precision at the cellular and molecular levels, reducing their toxicity and making them biocompatible. To reduce their toxicity, biological components can be used for their construction. Biological hybrid systems have recently emerged as alternatives to increase biocompatibility. Self-propelled nanorobots are also of great interest as they can reduce the need for external propulsions.
Once their limitations are reduced, and they become ready to be put into medical use, these nanorobots can revolutionize healthcare and have the potential to establish a new era in the diagnosis and therapy of cancer. Moreover, these nanorobots can also be used in theranostics - a single nanorobot performing diagnosis and therapy, simultaneously.

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