Research on: Micro and Nano-motors: The New Generation of Drug Carriers

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***Abstract*—Micro- and nano-motors are gaining popularity as cutting-edge drug delivery platforms because they provide benefits such quick drug delivery, deep tissue penetration, and motion controllability . They can be directed toward the area of interest by exogenous (such as ultrasonography, magnetic fields, or light) or endogenous (such as chemotaxis) stimuli. (1) Additionally, in order to enhance drug targeting, these stimuli can be employed to cause the release of a therapeutic payload when the motor reaches a certain region. Micro- and nanomotors (MNMs) are micro/nanoparticles capable of independent motion in complex fluids powered by various energy sources(2,4,5,8) They have attracted increasing attention due to their great potential in applications ranging from environmental science to biomedical technology. In recent decades, the field has developed rapidly, and many important innovations have occurred involving global scientists(10,11,12)**

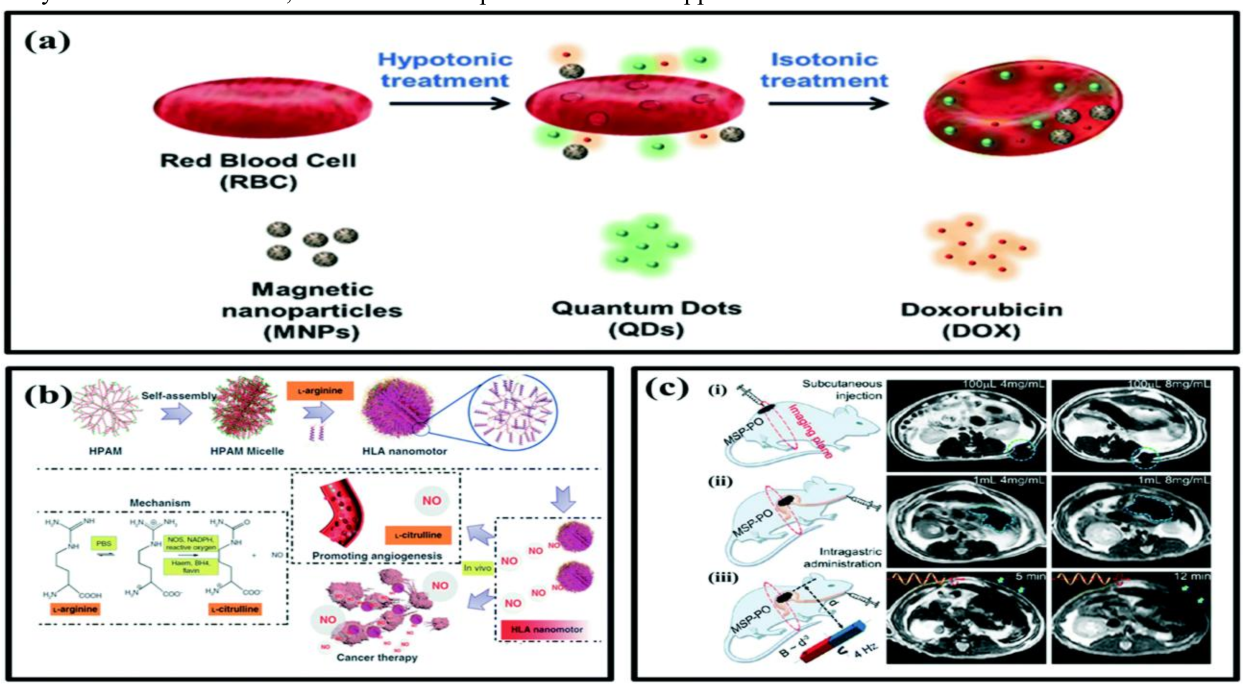
***Index Terms*—Micromotors, Endogenous, Controllability, Nanoparticles, liposomes, nanocrystals, nanotubes etc.**

I. INTRODUCTION

Small-scale living things have the ability to transform a variety of energies into mechanical work. Many organisms contain sensitive biomolecular motors that are in charge of energy conversion and movement that occurs at both a molecular and a macroscopic scale in order to maintain the basic functioning of the cell and respond to environmental changes(1) . On the other hand, human technology is also developing swiftly, and we are becoming increasingly adept at harnessing various power sources and turning them into mechanical work. (2) In the current day, we are able to create a range of effective machines like combustion engines and electric motors and utilize them to transform the world, unlike the old times when our forefathers could only move cattle or horses for work. Specifically at the microscopic level (3)

Since the introduction of the first sustained release systems in 1952, drug delivery methods have undergone significant evolution. Self-regulating drug release carriers and the first drug delivery nanostructures were created in the 1980s(4). Since then, research in this area has been concentrated on enhancing the targeting and systemic absorption of those carriers as well as on researching various nanoparticle-based medication formulations, issues that have been extensively discussed in the literature(5) Numerous Nano carriers, such as inorganic, polymeric, liposomes, Nano crystals, nanotubes, and dendrimers, have been investigated for use in therapy and many of them have already received FDA approval to treat conditions like neurovascular diseases, neurological cancers, and neurodegenerative diseases.(6) Their diameters range from 5 to 200 nm. New carriers with lower drug doses and protection from efflux or degradation have been developed as a result of research into their pharmacokinetics. To boost their specificity and circulation time, the majority of these nano carriers include complex surface bio functionalization, coatings like polyethylene glycol (PEG), or biomimetic alterations.(7) Nevertheless, those carriers still face difficulties with their targeting (currently, only 0.7% - on average - of the administered nanoparticle dose is found to be delivered to a solid tumour, penetration, drug loading, and subcellular delivery(8). Other type of drug carriers are the cellular ones, which have many advantages such as the ability to encapsulate higher amounts of drugs within their membrane, to interact with other cells/tissue and are more biocompatible compared to the mentioned Nano carriers, but they do not possess controlled motion to penetrate tissues or to perform actuation tasks[9]. Micro- and nano-motors are emerging to overcome these obstacles as a new generation of targeted drug delivery systems because they combine the advantages of previous drug carriers (e.g drug protection, selectivity, biocompatibility) with the ability to swim and penetrate tumour tissues and be equipped with special activation mechanisms to trigger drug release at the right time/space.[10] They can also be easily operated for in vivo imaging, detection of molecules from the surrounding environment, and/or occupies individual cells. The Nano motors can be designed to move through the body's fluids and tissues, and can even penetrate cellular membranes to deliver drugs directly to the target site. This targeted drug delivery approach has the potential to improve the efficacy of drug therapies while minimizing side effects. [11]

One of the main challenges in developing Nano motor drug delivery systems is ensuring their safety and biocompatibility, as well as designing motors that can withstand the harsh conditions of the body's environment. However, advances in nanotechnology and materials science are making it increasingly possible to create reliable and effective Nano motor drug delivery systems for a range of medical applications. [10,11]



Synthetic micromotors

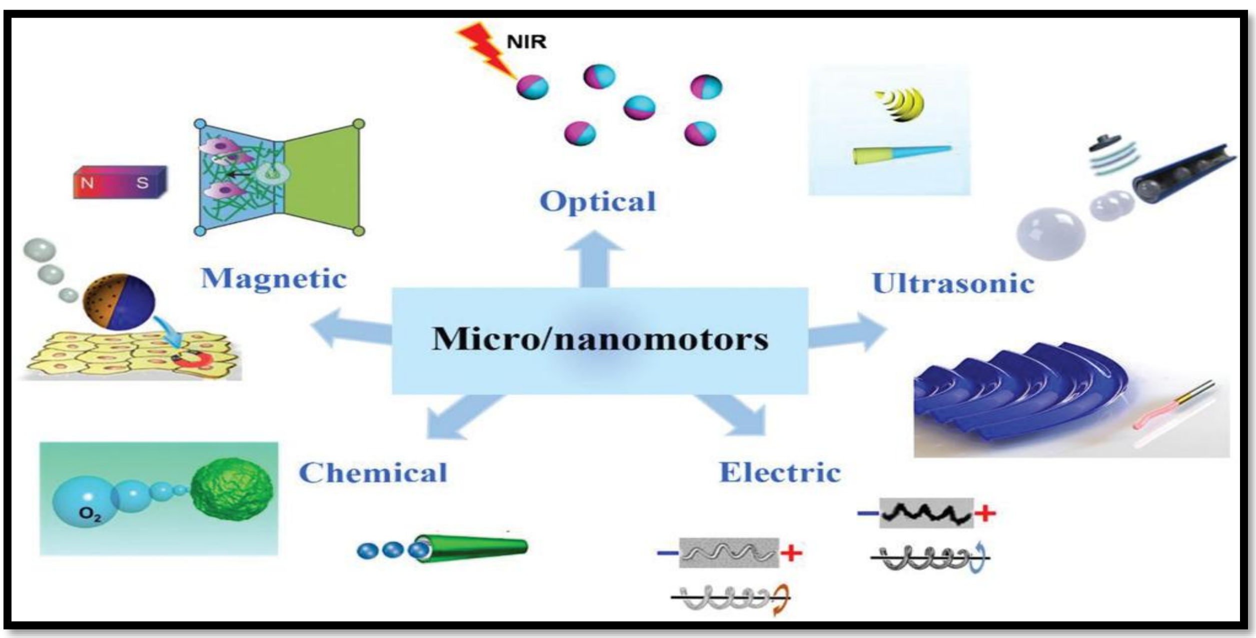
The most common synthetic micro motors are catalytic, which mainly had biomedical applications limited to proof of concept. Because they use toxic fuels, they cannot be used in life scenarios, unless the catalyst material and fuel are replaced by biocompatible ones. Some companies were designed to run small engines on bio-available fuels such as glucose or urea. However, the required concentration levels of these fuels were much higher than physiological levels in most of the reported work[9,10]. In addition, speeds these motors were very low, averaging a few micrometers per second. There are still many companies were performed to increase speed, directionality and enzymatic motor activity for example, electro active polymers for encapsulating larger amounts of enzymes or hollow mesoporous structures increase the reactive surface area [11,12]. Alternatively, materials that degrade in slightly acidic environments may such as zinc, manganese or calcium carbonate have also been used to make micro/Nano motors that can used in environments such as the stomach or near cancer cells, both of which have a pH below 7. Externally powered synthetic micro/Nano motors that can be steered to a target area The category of synthetic micro motors also includes external magnetic fields, ultrasound or light.[12] These micro motors can also be made of different materials and with different functions. They can be operated biomolecules or chemical substances that perform the same functions as catalytic molecules. They have better handling but as mentioned above, they need external control, which can be controlled in three dimensions. Therefore, Appropriate imaging techniques are required to track them, as they do not enter the area of interest by themselves, in the following sections, we describe specific jobs in which drugs or other therapeutic agents are released from the cargo has been demonstrated using chemically or physically actuated micro- and Nano motors.

Types of Nano motor Drug Delivery System

There are various types of Nano motor drug delivery systems, which can be classified based on the type of motor used and the mechanism of propulsion. Here are some of the most common types of Nano motor drug delivery systems[13]

1. Electrically propelled Nano motors: These motors are propelled by an electric field, which can be generated by an external power source or by a chemical reaction. Electrically propelled Nano motors have been shown to be effective in drug delivery applications, including targeted drug delivery to cancer cells.
2. Magnetic propelled Nano motors: These motors are propelled by a magnetic field which can be generated by an external magnet or by the application of an alternating magnetic field. Magnetically propelled Nano motors have been used for targeted drug delivery and have been shown to be effective in cancer treatment.
3. Chemically propelled Nano motors: These motors are propelled by a chemical reaction, such as the reaction between hydrogen peroxide and catalase. Chemically propelled Nano motors have been used for targeted drug delivery and have shown promise in applications such as wound healing and tissue engineering.
4. Hybrid Nano motor systems: These systems combine multiple types of propulsion mechanisms, such as electric and magnetic fields, to achieve greater control over the movement and targeting of the motors. Hybrid nanomotor systems have been shown to be effective in drug delivery and other biomedical applications.

In addition to these propulsion mechanisms, nanomotor drug delivery systems can also be classified based on the type of drug delivery mechanism used. For example, some nanomotor systems use a passive diffusion mechanism, while others use an active transport mechanism, such as endocytosis or phagocytosis. Overall, the type of nanomotor drug delivery system used depends on the specific application and the desired properties of the drug delivery system.



Advantages and disadvantages of nanomotor drug delivery system

Advantages:

Nanomotor drug delivery systems offer several advantages over traditional drug delivery methods, including:

1. Targeted drug delivery: Nanomotor can be designed to specifically target and deliver drugs to certain cells or tissues within the body, reducing the risk of side effects and increasing the effectiveness of the treatment.
2. Controlled drug release: Nanomotor can be engineered to release drugs in a controlled manner, either over a prolonged period or in response to specific stimuli such as changes in pH or temperature.
3. Increased drug bioavailability: Nanomotor can enhance the bioavailability of drugs by protecting them from degradation and improving their solubility, thus increasing their efficacy.
4. Reduced toxicity: By delivering drugs directly to the target site, nanomotor drug delivery systems can reduce the overall dosage required, which can help to minimize toxicity and side effects.
5. Improved pharmacokinetics: Nanomotor can improve the pharmacokinetics of drugs by increasing their circulation time and facilitating their transport across biological barriers, such as the blood-brain barrier.
6. Efficient drug delivery: Nanomotor drug delivery systems can potentially improve the efficacy of drugs by enabling them to reach their targets in a more efficient manner.
7. Lower dosage requirements: With targeted delivery, the amount of drug required to achieve a therapeutic effect may be reduced, which can potentially minimize side effects and reduce costs.
8. Potential for combination therapies: Nanomotor drug delivery systems can enable the delivery of multiple drugs to a specific site, which can be useful for combination therapies.

Disadvantages:
While nanomotor drug delivery systems offer several advantages over traditional drug delivery methods, there are also some potential disadvantages to consider:
1. Complexity and cost: The development of nanomotor drug delivery systems is a complex and expensive process, which may limit their widespread use and accessibility.
2. Safety concerns: The safety of Nano motors in the human body is still being studied, and there are concerns about their potential toxicity and long-term effects on health.
3. Regulatory challenges: The regulation of Nano motors as medical devices is still evolving, which could present challenges for their commercialization and clinical use.
4. Manufacturing challenges: The manufacture of Nano motors on a large scale can be challenging and may require specialized equipment and expertise.
5. Which may not be sufficient for some therapies or patients with higher drug requirements.

Uses of Nanomotor in Treatment of Various Disease [13,14]

Nanomotor technology has the potential to revolutionize disease treatment in various ways. Some of the potential uses of nanomotors in disease treatment include:

1. Cancer treatment: Nanomotors can be used to deliver chemotherapy drugs directly to cancer cells, reducing the exposure of healthy cells to toxic drugs and minimizing side effects.

2. Targeted drug delivery: Nanomotors can be designed to target specific cells or tissues, such as neurons in the brain, offering a highly specific and effective means of drug delivery.

3. Diabetes management: Nanomotors can be used to deliver insulin to diabetic patients, enabling more precise control of blood glucose levels and reducing the need for frequent injections.

4. Cardiovascular disease treatment: Nanomotors can be used to deliver drugs or imaging agents to the heart or blood vessels, improving diagnosis and treatment of cardiovascular diseases.

5. Infectious disease treatment: Nanomotors can be designed to deliver antimicrobial agents to infectious agents, such as bacteria or viruses,

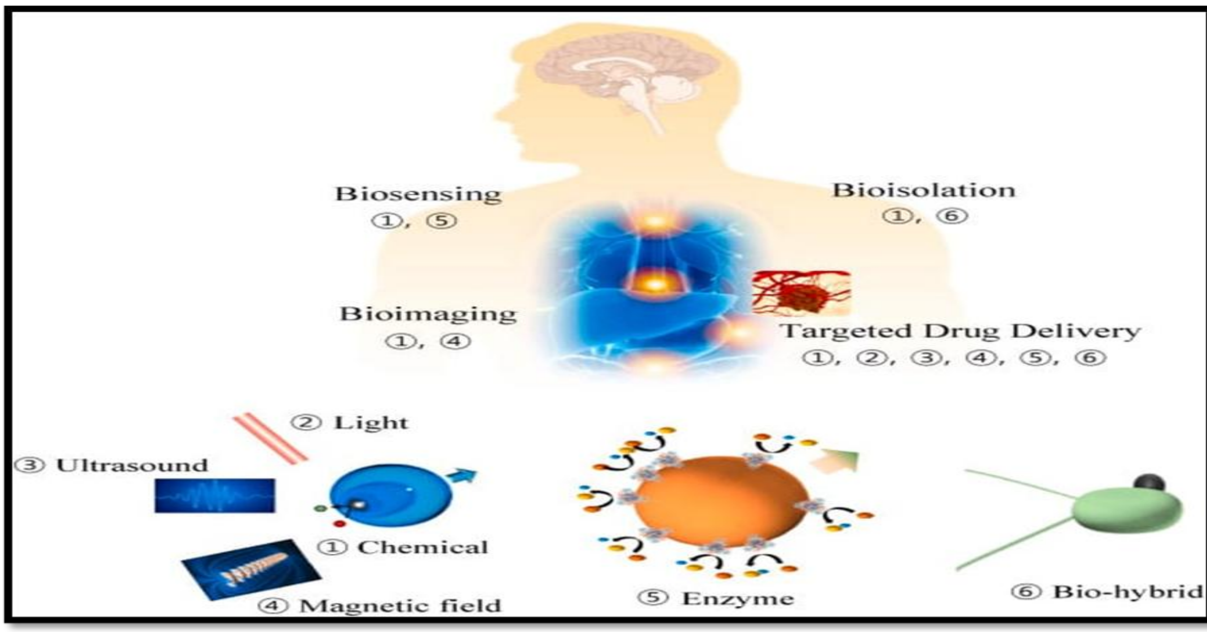
improving the efficacy of treatments and reducing the risk of resistance.

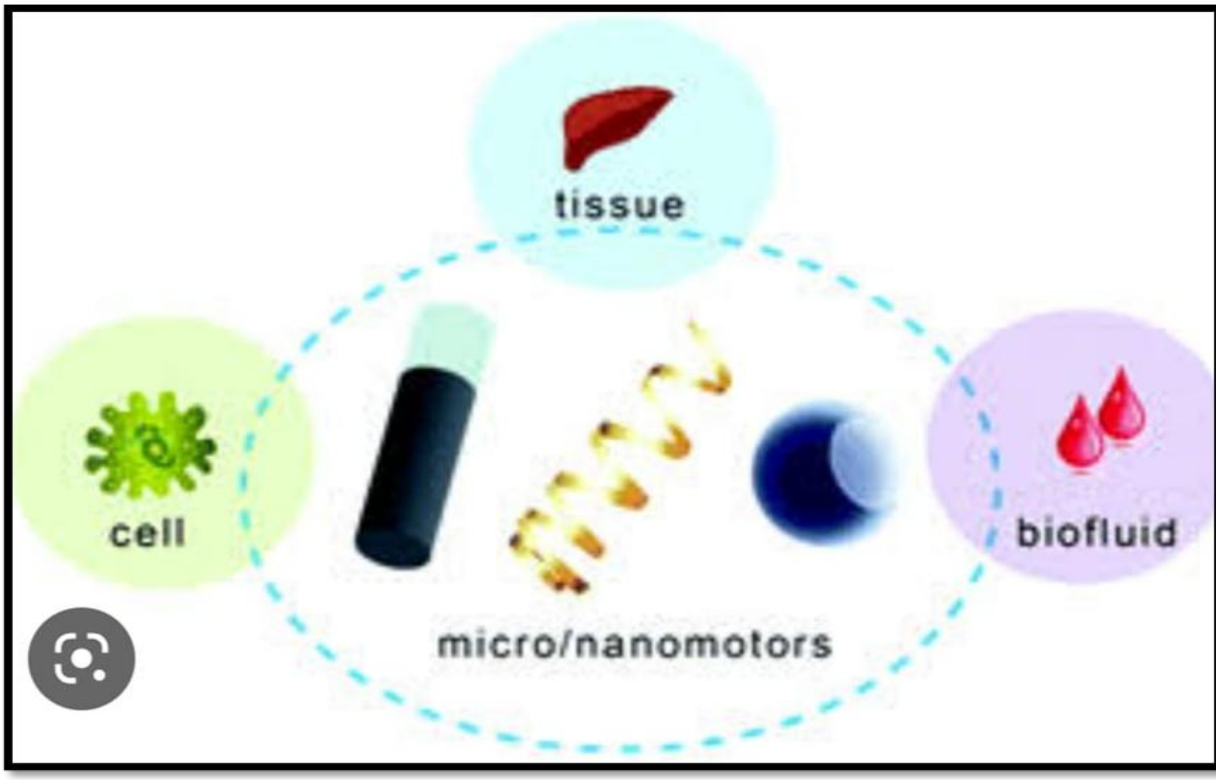
6. Neurodegenerative disease treatment: Nanomotors can be used to deliver drugs to the brain to treat neurodegenerative diseases such as Alzheimer's or Parkinson's, potentially slowing or even reversing the progression of these diseases.

7. Infectious diseases: Nanomotors can be designed to deliver antimicrobial agents to infectious agents, such as bacteria or viruses, improving the efficacy of treatments and reducing the risk of resistance.

8. Genetic diseases: Nanomotors can be used to deliver gene therapies directly to specific cells or tissues, potentially offering a cure for genetic diseases such as cystic fibrosis or sickle cell anaemia.

9. Overall, nanomotor technology holds great promise for the development of highly targeted and effective therapies for a range of diseases, and could have a significant impact on the future of medicine.





II. NANOMOTOR USED IN BLOOD VESSELS:

Blood vessels can be found in almost every corner of the human body. The vascular system maintains cellular homeostasis through a complex network of arteries, capillaries, and veins. Administration into blood vessels is mostly accomplished by intravenous injection, which enables the drug to be passively transported to the target site with the flow of blood. (15) Toxicity and side effects cannot be ignored when the drugs take effect. A nano/micromotor delivery system could reduce toxicity and side effects and improve therapeutic efficiency in the blood vessels.(13,14)

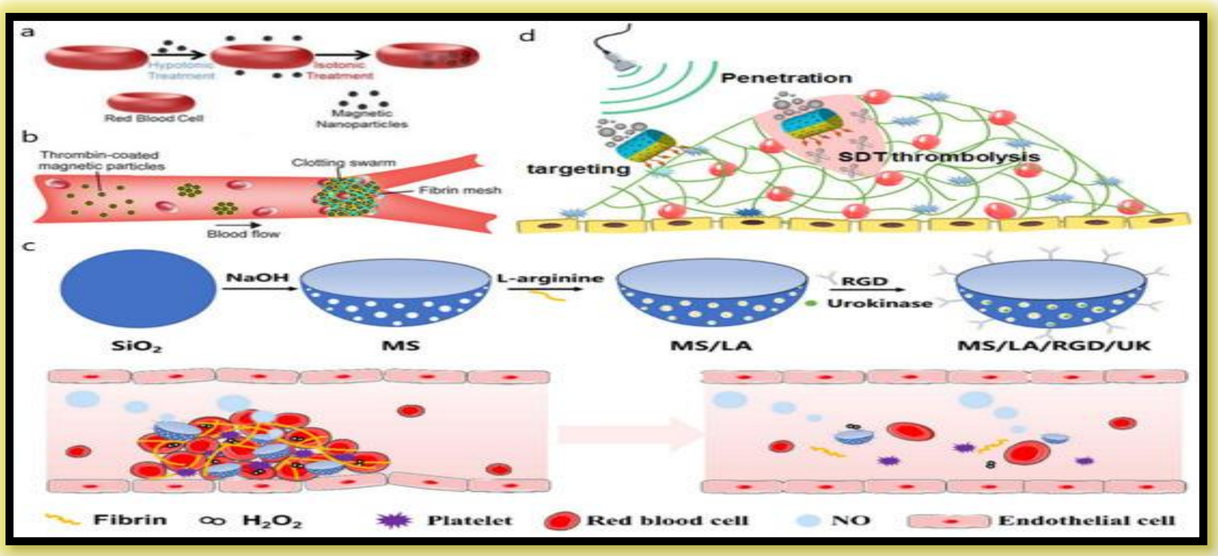
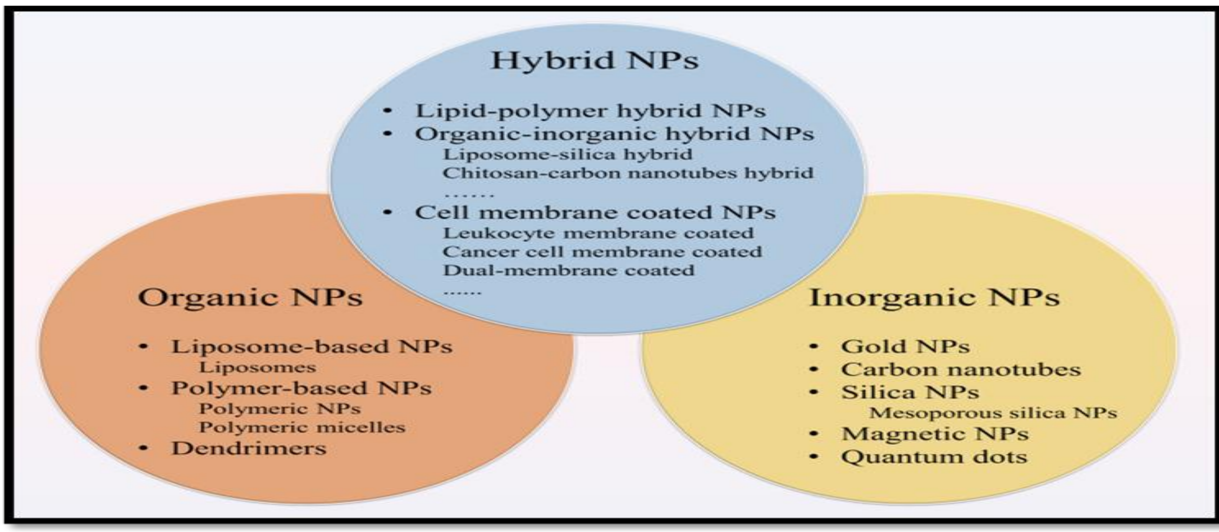


Figure. Nano/micromotors in the blood vessels.

(**a**) Fe_3O_4 nanoparticle-loaded RBC motors could be propelled by ultrasound fields.
(**b**) Superparamagnetic motors coated with thrombin could agglutinate in a certain magnetic field and block the vessel.
(**c**) The LA of NO-driven silica motors with bowl-shaped mesoporous could react with ROS to produce NO to propel the motor.
(**d**) The ejection of O_2 bubbles and the cavitation effect produced by the ultrasonication of O_2 could be the power source of the Janus rod (JR)-shaped motors.
Current problems and remaining studies:
(A) Different blood vessels have different blood velocities, so strong propulsion does not apply to all blood vessels. In the future, more flexible and adjustable micromotors will be needed for variable blood vessels (such as capillaries. We may refer to the streamlined structure of fish in the design of micromotors.
(B) The real-time imaging of micromotors in blood vessels has become an urgent problem to be solved. We suggest that future works may find a strong signal source, such as the magnetic micro swarm for MRI contrast enhancer, which is harmless to the human body. It could be a part of the micromotor, and then through the instrument in vitro, it could provide imaging for the precise operation of micromotors.



(C) The micromotor could rapidly target damaged blood vessels. The vessels in different normal tissues, such as hepatic sinusoids and glomeruli, could also be a target. We suggest that future works could add specific recognition components to the micromotor to target liver and kidney tissues and realize the monitoring of liver and kidney function in the future.

III. NANOMOTOR USED FOR THE TREATMENT OF CANCER

Finding new and innovative treatments for cancer is a major problem across the world. [15] With an increase in the number of methods that can treat cancer and the concept of an individualized treatment, the therapeutic efficacy of some malignant tumours has greatly improved. Chemotherapy is a conventional and widely used cancer treatment method. While chemotherapy works through a number of different mechanisms, its major function includes indiscriminately killing vigorously growing cells, including tumor and normal cells, which causes some serious side effects including bone marrow suppression, hair loss, and gastrointestinal reactions Therefore, developing drugs that more accurately target tumour cells, instead of normal cells, has been the purpose of a large proportion of cancer-related research in the past few decades.[16] Although the emergence of targeted therapy has made great progress in precision therapy, there are still many unavoidable adverse effects, and the development of drug resistance has always been a problem. Currently, cancer remains the second leading cause of death, and current therapies for many cancers are inadequate. Hence, increasingly more studies are seeking precise therapy of cancer and solutions for drug resistance.[17]
The NPs used in medical treatment usually have specific sizes, shapes, and surface characteristics as

these three aspects have a major influence on the efficiency of the nano-drug delivery and thus control therapeutic efficacy. NPs with a diameter range of 10 to 100 nm are generally considered suitable for cancer therapy, as they can effectively deliver drugs and achieve enhanced permeability and retention (EPR) effect[18]. Smaller particles can easily leak from the normal vasculature (less than 1–2 nm) to damage normal cells and can be easily filtered by kidneys (less than 10 nm in diameter, while particles that are larger than 100 nm are likely to be cleared from circulation by phagocytes. Moreover, the surface characteristics of NPs can influence their bioavailability and half-life.[17,18] For instance, NPs that are coated with hydrophilic materials such as polyethylene glycol (PEG) lessen the opsonization and therefore avoid clearance by the immune system. Therefore, NPs are generally modified to become hydrophilic, which increases the time period of drugs in circulation and enhances their penetration and accumulation in tumours Collectively, the various characteristics of NPs determine their therapeutic effect in cancer management. [18] Different types of NPs for cancer therapy are shown in Figure 1 and the following text will describe their respective advantages in tumour treatment.

1. ORGANIC NPs

Organic NPs have been widely explored for decades and contain many types of materials. Liposome, the first nano-scale drug approved for clinical application consists of an outer lipid layer and a core entrapping either hydrophobic or hydrophilic drug. Liposomes can carry out many functions by modifying the lipid layer structure, including imitating the biophysical characteristics (e.g., mobility and deformation) of living cells, which can help achieve the purpose of more effective therapeutic drug delivery. With decades of research, the development of liposomes has gone through several generations. With regard to cancer therapy, liposomes provide a good platform for in vivo delivery of many anti-tumour drugs, such as doxorubicin and paclitaxel, among other chemotherapeutic agents, as well as nucleic acids.[15,16] In the field of breast and prostate cancer the application of liposomes has been increasingly common Multiple paclitaxel liposomes have been demonstrated to have higher anti-tumour efficiency and improved bioavailability compared to free paclitaxel. Liposomal doxorubicin has been proven to reduce cardiotoxicity and has comparable efficacy in breast cancer. Furthermore, liposome-based nano systems have also offered an option for drug combination, which can enhance the therapeutic effect and even reverse the drug resistance. [17]Now, a days, more varieties of liposome-based drugs have entered into clinical use for cancer treatment. Polymer-based NPs are another type of NP with specific structural arrangements for drug delivery formed by different monomers. Polylactic-co-glycolic acid (PLGA), a common polymeric NP, encompasses copolymerization of glycolic acid and lactic acid. Given its better biocompatibility and biodegradation, as well as the EPR effect, PLGA is widely used as a carrier for drug delivery Additionally, dendrites are another class of polymers that have been applied to nano medicine.[18]They are versatile and biocompatible macromolecules that are characterized by a three-dimensional branch structure. Their multiple functional groups on the surface enhance.

The capability of loading and delivering therapeutic agents. Furthermore, polymeric micelles, which are characterized by polymer self-assembly into nano-aggregates as they are composed of amphiphilic copolymers, constitute another kind of widely investigated polymer NPs the hydrophobic core enables the insoluble anticancer drugs to be absorbed and delivered smoothly, while the hydrophilic segment increases stability, thus reducing the uptake of the drug by the reticulo- endothelial system and prolonging their time period in circulation.

2. INORGANIC NPs

Inorganic NPs have the advantages of a higher surface area to volume ratio. They have a wide and easily modified surface conjugation chemistry and facile preparation; although this usually occurs at the expense of poorer biocompatibility and bio degradability.[19]The inorganic NPs that have been studied include gold NPs (AuNPs), carbon nanotubes (CNTs), quantum dots, magnetic NPs (MNPs), and silica NPs (SNPs). AuNPs are the most widely studied inorganic NPs, and mixed monolayer-protected clusters based on the gold core are considered to be a promising candidate in the drug delivery system. The gold core is inert and non-toxic, and surface-functionalized AuNPs have been proven to enhance drug accumulation in tumours as well as to overcome the drug resistance. Moreover, AuNPs are thought to be involved in multimodal cancer treatment including gene therapy, photothermal therapy and immunotherapy carbon nanotubes are a type of tubular material that have been shown to have broad potential in the drug delivery field due to their unique biological, physical, and chemical properties.[19,20] As a result, they have been used to deliver anticancer agents including doxorubicin, paclitaxel, and methotrexate siRNA for a variety of cancers Meanwhile, CNTs produce heat when they are exposed to near-infrared radiation, which could be applied to thermal ablation for cancer therapy .Mesoporous silica nanoparticle carriers are a type of SNPs which are suitable for drug delivery .The large internal pore volume enables them to encapsulate the maximum amount of anticancer drugs, and the supramolecular components act as a cap, allowing capture and release of drugs . Due to better pharmacokinetics and treatment efficacy, as well as high stability, SNPs are considered one of the best vehicles for drug delivery. Moreover, porous silicon NPs have shown great potential in immunotherapy as its immunoadjuvant properties include promotion of antigen cross presentation, polarization of lymphocytes and secretion of interferon-γ (IFN-γ) Magnetic NPs (MNPs) used for drug delivery usually contain metal or metal oxide NPs. In order to improve the stability and biocompatibility, MNPs are commonly coated with organic materials, including polymers and fatty acids.[20] They have been shown to demonstrate high efficacy in chemotherapy and gene therapy for cancer treatment. Furthermore, magnetic hyperthermia using MNPs can achieve thermal ablation of tumours, which offers alternative cancer treatment.

3. HYBRID NPs

As both organic and inorganic NPs have their own advantages and disadvantages, combining the two in a single hybrid drug delivery system endows the multifunctional carrier with better biological properties that can enhance treatment efficacy as well as reduce drug resistance .Lipid-polymer hybrid NPs, which consist of an inner polymeric core and a lipid shell, have been demonstrated to be a promising drug delivery platform in the treatment of pancreatic cancer, breast cancer and metastatic prostate cancer.[21] This type of hybrid NPs combines the high biocompatibility of lipids with the structural integrity provided by polymer NPs, and are therefore capable of encapsulating both hydrophilic and hydrophobic drugs in order to achieve a better therapeutic effect Meanwhile, this system can be effectively internalized by cancer cells and avoids fast clearance by the reticulo endothelial system.[21,22] The combination of organic and inorganic hybrid nano materials is a common method of NP design. For example, a liposome-silica hybrid (LSH) nanoparticle consists of a silica core and a surrounding lipid bilayer and has been synthesized and shown to be valid in delivering drugs to kill prostate and breast cancer cells .The LSH nanoparticle has also been reported to offer a platform for the synergistic delivery of gemcitabine and paclitaxel to pancreatic cancer in a mouse model of the disease created an advanced nano-in-micro platform by assembling the porous silicon NPs and giant liposomes onto a microfluidic chip, and co-delivery of synthesized DNA nanostructures and drugs in this platform was proven to significantly enhance cell death of doxorubicin-resistant breast cancer cells.[23]Furthermore, CNTs and the chitosan hybrid NP used in the vectorization of methotrexate to lung cancer cells tend to increase anticancer activity while reducing drug toxicity on normal cells. Moreover, half-shells of metal multilayers (such as manganese and gold) and PLGA hybrid NPs have the potential of combining targeted drug delivery and hyperthermia, which can enhance the destruction of tumour cells.[21,22] The hybridization of natural biomaterial with organic or inorganic NPs is another method for NP design. For example, cell membrane coating nanotechnology is emerging and has increasingly gained more attention. This technology tends to bestow the NPs with biological characteristics directly by coating NPs with naturally derived cell membranes, which enhances the potency and safety of conventional NPs.[23] The coatings include cell membranes derived from leukocytes, red blood cells, platelets, cancer cells, and even bacteria have shown that coating nano porous silicon particles with a cell membrane which is purified from leukocytes can prevent the nano-carrier from clearance by phagocytes, and the characteristics of this hybrid particle allow the drug to have extended time period in circulation, leading to increased accumulation in the tumour. [23]Similarly, some studies have utilized cancer cell membrane-cloaked mesoporous silica NPs for cancer treatment, which improves the stability and targeting ability of nano-carriers. Moreover, the development of dual-membrane coated NPs can further enhance the function of NPs. For instance, erythrocyte-platelet hybrid and erythrocyte cancer hybrid membrane-coated NPs were proven to exhibit better stability and longer circulation life proposed a multistage NP delivery system to achieve deep penetration into tumours by changing the size and characteristics of NPs at different stages. In their study, the size change of NPs was achieved by protease degradation of the cores of 100-nm gelatine NPs within the tumour microenvironment in order to release 10-nm quantum dot NPs. [24]

Mechanisms of Targeting

Targeting of cancer cells specifically is a vital characteristic of nano-carriers for drug delivery, as it enhances the therapeutic efficacy while protecting normal cells from cytotoxicity. Numerous studies have been carried out to explore the targeting design of NP-based drugs. In order to better address the challenges of tumour targeting and the nano-carrier system design, it is crucial to first understand tumour biology and the interaction between nano-carriers and tumour cells. The targeting mechanisms can be broadly divided into two categories, passive targeting and active targeting.[25]

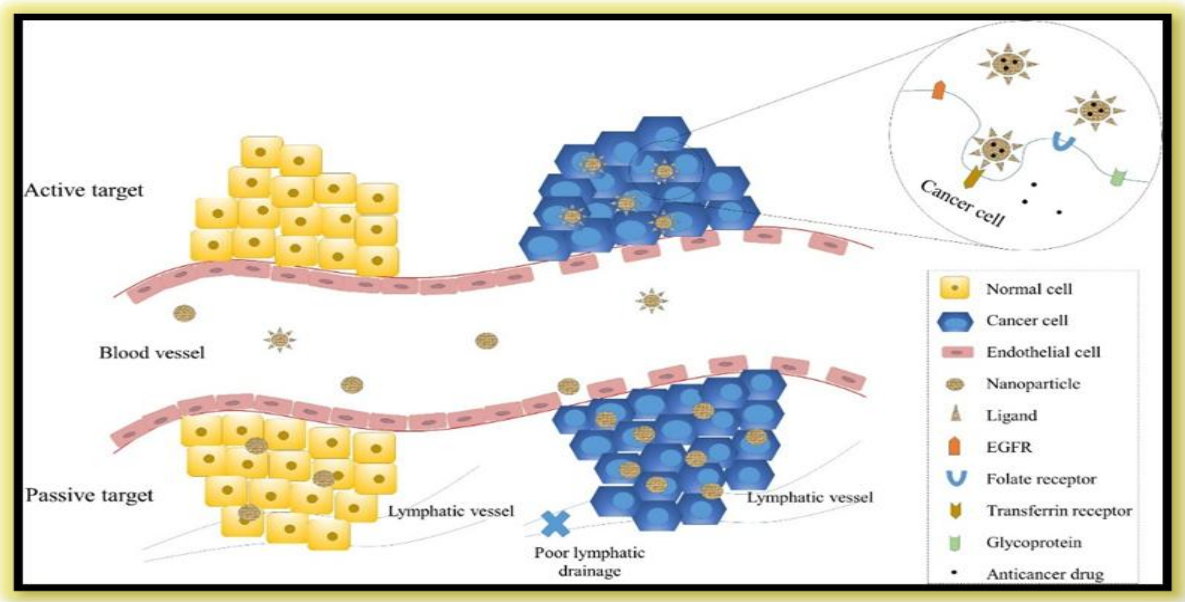
➢ Passive targeting

Passive targeting is designed to utilize the different characteristics of tumour and normal tissue. In passive targeting, the drugs are successfully delivered to the target site in order to play a therapeutic role. High proliferation of cancer cells induces neovascularization, and large pores in the vascular wall lead to a worsening perm selectivity of tumour vessels compared to normal vessels.[21,22] The rapid and defective angiogenesis enables macromolecules, including NPs, to leak from blood vessels that supply the tumour and accumulate within tumour tissue. Meanwhile, the poor lymphatic drainage associated with cancer increases the retention of NPs, allowing the nano carriers to release their contents to tumour cells. These processes cause the EPR effect, one of the driving forces of passive targeting.[20]The EPR effect is influenced by the size of NPs, as many studies have demonstrated that smaller NPs have better penetrability but do not leak into normal vessels. On the other hand, larger particles are more likely to be cleared by the immune system. In addition to the EPR effect, the tumour microenvironment is also an important factor in the passive delivery of nanomedicines.

Glycolysis is one of the metabolic characteristics of cancer cells and is the main source of energy for cancer cell proliferation.[25] Glycolysis yields an acidic environment and reduces the pH of the tumour microenvironment. Subsequently, some pH-sensitive NPs are triggered by the low pH level and are able to release drugs within the vicinity of cancer cells. However, there are some limitations with regards to passive targeting, including non-specific drug distribution, non-universal existence of the EPR effect and different permeability of blood vessels across various tumours.

➢ Active targeting

Active targeting specifically targets cancer cells through direct interactions between ligands and receptors. The ligands on the surface of NPs are selected to target the molecules that are overexpressed on the surface of cancer cells, which allows them to distinguish targeted cells from healthy cells. The interaction between ligands on NPs and the receptors on the surface of cancer cells induces receptor-mediated endocytosis, which allows internalized NPs to successfully release therapeutic drugs.[23,24] Therefore, active targeting is particularly suitable for macromolecular drug delivery, such as proteins and siRNAs. The types of targeting moieties include monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates. These ligands specifically bind to receptors on targeted cells, and the widely investigated receptors include transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR).



Targeting to Cancer Cells

Transferrin, a type of serum glycoprotein, functions to transport iron into cells. Transferrin receptors are overexpressed in most solid tumour cells and are expressed at low levels in normal cells. Thus, transferrin-conjugated NPs are used as an active targeting method to deliver drugs for cancer treatment. Compared to unmodified NPs, transferrin-modified NPs have been shown to exhibit higher cellular uptake efficiency and enhanced intracellular delivery of drugs [14,16]. Moreover, evidence indicates that transferrin-conjugated polymeric NPs play a significant role in overcoming drug-resistant chemotherapy. Folic acid, a type of vitamin, is essential in nucleotide synthesis. It is internalized by a folate receptor that is expressed on few normal cell types. However, the alpha isoform of folate receptor (FR-α) is overexpressed in approximately 40% of human cancers, while FR-β is expressed on the surface of hematopoietic cancers. Thus, the folate receptor targeting strategy by folate-conjugated nano materials has been widely used for cancer treatments. In addition, cancer cells usually express various types of glycoproteins, including lectins, which are non-immunological proteins that recognize and specifically bind to certain carbohydrates. [20] Targeting cancer cell-surface carbohydrates by lectins conjugated to NPs constitutes the direct lectin targeting pathway, while inversely targeting lectins on cancer cells using carbohydrates moieties that are incorporated into NPs is referred to as the reverse lectin targeting pathway. Epidermal growth factor receptor is a member of the Ebb family of tyrosine kinase receptors.[21] EGFR, which is overexpressed in varieties of cancers, is involved in several processes of tumour growth and progression and has already been utilized as a target for cancer treatment. For example, targeting human epidermal receptor2 (HER-2) is a common therapy for HER-2 positive breast and gastric cancer. Hence, NPs that have been designed to incorporate modified ligands that bind to EGFR in order to target EGFR-overexpressed cancer cells is a promising method of drug delivery. Furthermore, conjugating two cancer-specific ligands into a single NP is another way of active targeting, as it can help improve target specificity.

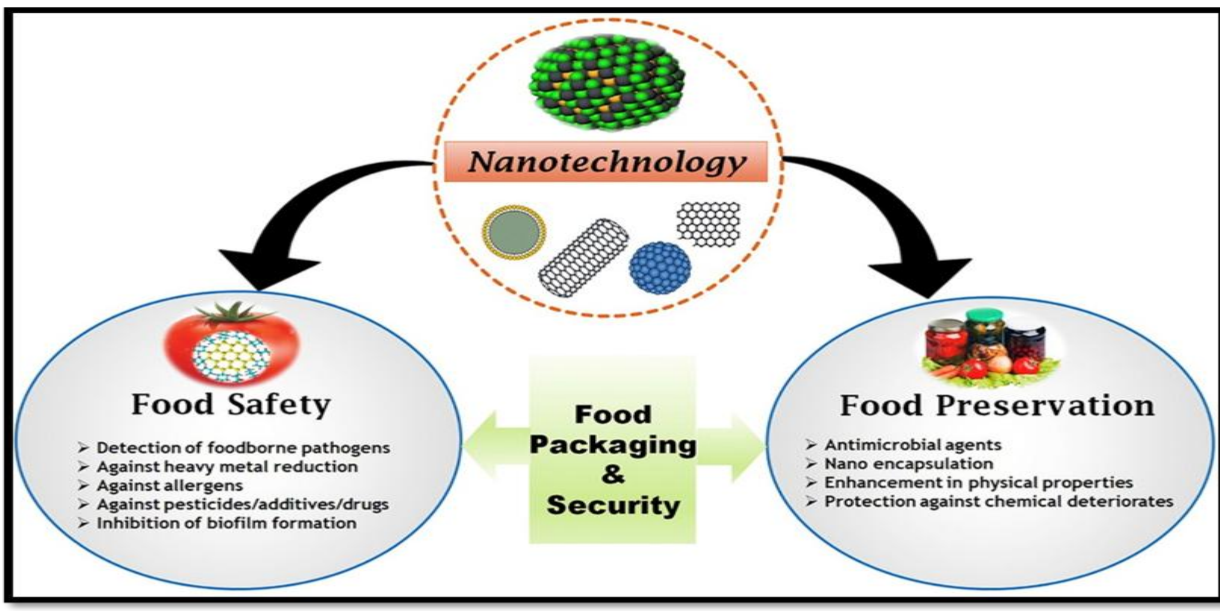
Benefits of Nanotechnology

Nanotechnology has a wide range of potential usages that could produce advancements in medical treatment, pharm tech, food transportation and the electronics industry[18] .A nanomotor, the scale used for nanotechnology, is one billionth of a meter. For a sense of scale, a sheet of paper is 100,000 nanomotor thick. As you can see, nanotechnology, any technology that operates between 1-100 nanomotors, works on an unfathomably small scale. However, despite many positive signs that the technology has possible societal impact, there are some objectors who oppose the science's future on ethical and legal grounds. However, many of their arguments are vaguely defined and lack substantiative evidence.[20] What is certain is that nanotechnology is at the forefront of technology and industry. The science has many specific benefits that are already being researched to improve heart health, provide more efficient solar power and elongate the shelf life of vegetables.

Nanotechnology in the medical industry

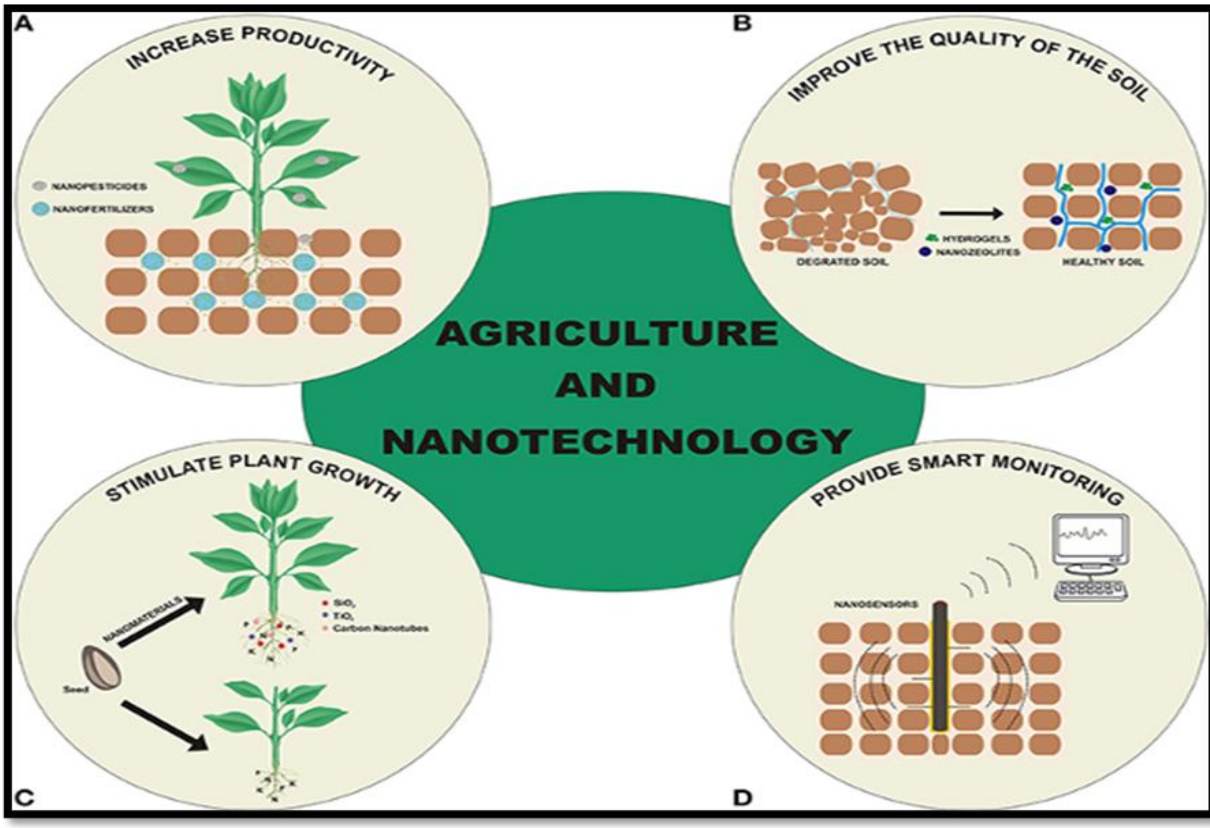
Recent research done by scientists at the University of Bath and Bristol has used nanotechnology to develop a pacemaker that could help prevent heart failure and extend the lives of those who have suffered from cardiovascular disease. The study explains that the heart beats in correlation with the lungs, causing rhythmic patterns that allow the heart to function efficiently.[11,15] That is to say, our rate of breathing directly influences to our heart rate. Cardiovascular disease throws off variations in heart rate that synchronize with lung inflations, causing a discordance that can lead to heart failure[5] The device created by scientists, an updated pacemaker, enhances the heart's ability to pump blood efficiently and saves energy. The pacemaker the team created is miniaturized, about the size of a postage stamp, and they expect to be able to significantly extend the life of those who experience heart failure.[21,18]

Traditional pacemakers are set to keep heartbeats at a constant rate, whereas the heart does not function that way naturally within the body. Giving pacemakers the ability to work closer with the lungs and form natural rhythms with the body puts less stress on the muscle.[12,25]



Nanotechnology in Agriculture

In food science, the use of nanotechnology can potentially elongate the life of fruits and vegetables. This could be achieved, for example, by putting nanoparticles of silver into foods to work as an antibacterial agent. These nanoparticles would not be a large enough component of the food to have a harmful effect or alter the flavour. In fact, many food manufacturers already use nanotechnology in food. The Food and Drug Administration doesn't have a specific stance on nanotechnology. However, the organization has recently requested that companies using nanotechnology consult it to discuss the product.[9,10] This could include a wide range of products including medical services, foodstuffs and cosmetics, though the FDA is specifically focused on the latter two. It would appear for the moment the FDA mainly wants to be considered a consultant when companies opt to use nanotechnology. Skin moisturizers, sunscreen and other cosmetics have been using nanoparticles for some time, but the FDA generally has less control over this industry.[14,15]



Nanotechnology in society

Perhaps the most intriguing aspect of nanotechnology in regard to agriculture is the potential for artificial photosynthesis to be utilized in regard to solar power. Scientists have used a device called a water splitter which allows hydrogen to be produced to create power when the sun is not directly shining. But this device relies silicon, which corrodes quickly when put in contact with electrolytes, and therefore in the past has only been able to be used in short durations. [23,22] Using nanotechnology to develop solar energy could potentially increase sustainability. Scientists at the University of Stanford prevented a silicon-based water splitter from corroding by plating it with two nanometres of nickel. Plating the silicon cell with nickel has led to promising results, but additional testing is needed to make the fuelling method cost effective [24]. Nanotechnology is also being used to develop long-term environmental clean-up functions, specifically to help remove pollutants from air and water. This is being done by creating miniscule filters that collect toxic particles. The technology is also has been used in developments in the electronics, IT and transportation industries. [13,19]

Ethical and Legal Implication

Nanotechnology comes with some risks, specifically in regard to food, as products utilizing the technology haven't undergone heavy testing and are not currently subject to labelling. The reason organizations such as the FDA are yet to take a strong stance on nanotechnology products is because there is yet to be any definitive evidence that nanoparticles are a safety risk.[22,16] The organization wants to prudently catalyse and monitor product development, but does not have any reason to inhibit usage. However, some advocacy groups attest that the lack of labelling and regulation on nanoproducts has a harmful societal impact. [25] The focus of these groups, such as Friends of the Earth, is to change policy to have food products that use nanoparticles labelled. Additionally, the organization focuses on potentially toxic nanoparticles found in sunscreen and cosmetics.

IV. CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Sachin B Somwanshi, Ramdas T Dolas, Vikrant K Nikam., Floating multiparticulate oral sustained release drug delivery system. J. Chem. Pharm. Res., 2011; 3(1):536-547.

[2] Bafna, D., Ban, F., Rennie, P.S., Singh, K., and Cherkasov, A.,'Computer-Aided Ligand Discovery for Estrogen Receptor Alpha', International Journal of Molecular Sciences, 21(12), 2020, 1–49.

[3] Torchilin, V. P., Multifunctional Pharmaceutical Nanocarriers, 2014, Springer.

[4] Bae Y. H., & Park, K., Handbook of Polymer Applications in Medicine and Medical Devices. Elsevier,2017.

[5] Davis, M. E., & Chen, Z. G., Nanoparticle therapeutics: an emerging treatment modality for cancer. Nature Reviews Drug Discovery, 7(9), 2008, 771-782.

[6] Farokhzad, O. C., & Langer, R., Impact of nanotechnology on drug delivery. ACS Nano, 3(1), 2009,16-20.

[7] Jain K. K., Drug Delivery Systems. Humana Press. 2008

[8] Kamaly, N., Xiao, Z., Valencia, P. M., Radovic-Moreno, A. F., & Farokhzad, O. C. Targeted polymeric nanoparticles for cancer gene therapy. Journal of Drug Targeting, 20(1), 2012,1-15.

[9] Das RJ, Baishya K, Pathak K, Recent advancement of lipid drug conjugate as nano particulate drug delivery system. Int Res J Pharm 4, 2013 ,128-131.43.

[10] Zhang, J.; Chen, Z.; Kankala, R.K.; Wang, S.-B.; Chen, A.-Z. Self-propelling micro-/nano-motors: Mechanisms, applications, and challenges in drug delivery. Int. J. Pharm. 2021, 596

[11] Parmar, J.; Ma, X.; Katuri, J.; Simmchen, J.; Stanton, M.M.; Trichet-Paredes, C.; Soler, L.; Sanchez, S. Nano and micro architectures for self-propelled motors. Sci. Technol. Adv. Mater. 2015, 16

[12] Purohit DK, Nandgude TD, Poddar SS, Nano-lipid carriers for topical application: Current scenario. Asian J Pharm 10: ,2016, 1-9.

[13] Ghasemiyeh,P. and Mohammadi-Samani, S. 'Solid Lipid Nanoparticles and Nanostructured Lipid Carriers as Novel Drug Delivery Systems: Applications, Advantages and Disadvantages', Research in Pharmaceutical Sciences, 13(4), 2018, 288–303.

[14] Garg R and Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res, 7: 2008; 1055-1066

[15] Rao PB, Kottan NA and Snehith VS. Development of gastroretentive drug delivery system of cephalexin by using factorial design. ARS Pharmaceutica 2005; 50:8-24.

[16] Dubey A, Prabhu P, Kamath JV Nano structured lipid carriers: A novel topical drug delivery system. Int J PharmTech Res 4: 2012,705-714.11.

[17] Gaba B, Fazil M, Khan S, Ali A, Baboota S, Nano structured lipid carrier system for topical delivery of terbina□ne hydrochloride. BullFac Pharmacy 53: 2015 ,147-159.44.

[18] Upreti T, Nanostructured Lipid Carrier System for the Treatment for Skin Disease-A Review. JSM Nanotechnol Nanomedicine 5: 2017, 1059.46.

[19] Fang CL, Al-Suwayeh SA, Fang JY, Nanostructured Lipid Carriers (NLCs) for Drug Delivery and Targeting. Recent Pat Nanotechnology, 7: 2012 ,41-55.45.

[20] Sharma, A. and Baldi, A., 'Nanostructured Lipid Carriers: A Review Journal', Journal of Developing Drugs, 7(2), 2018, 1–12.

[21] Tej, KVMS., Moin, A., Gowda, D.V., Karunakar, G., Patel, N.P., Kamal, S.S. 'Nano Structured Lipid Carrier Based Drug Delivery System', Journal of Chemical and Pharmaceutical Research, 8(2), 2016, 627–643.

[22] Rapalli, V.K.; Kaul, V.; Waghule, T.; Gorantla, S.; Sharma, S.; Roy, A.; Dubey, S.K.; Singhvi, G. Curcumin loaded nanostructured lipid carriers for enhanced skin retained topical delivery: Optimization, scale-up, in-vitro characterization and assess-ment of ex-vivo skin deposition. Eur. J. Pharm. Sci. 2020, 152.

[23] Pawar, R.P.; Rohane, S.H. Role of Autodock vina in PyRx Molecular Docking. Asian J. Res. Chem., 14, 2021,132–134.

[24] K. K. Jain, "Current status and future prospects of drug delivery systems," Methods in Molecular Biology, vol. 1141, 2014. pp. 1–56,

[25] National Nanotechnology Initiative (NNI)