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NANOROBOTICS BASED DRUG DELIVERY SYSTEMS: RECENT DEVELOPMENTS AND FUTURE PROSPECTS

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Abstract: The field of nanorobotics has made significant progress. Nanorobotics is a new field that has sparked a lot of attention among pharmaceutical researchers and drug delivery scientists. Nanorobots administer drugs to specific areas, seeking to make them far more effective and reducing the risk of unwanted side effects. These nanorobots are made of nanomaterials and will complete the mission. Nanomaterials are materials with a dimension of 1 to 1000 nanometers. Nanomaterials have holds great potential in drug delivery through passive or active targeting mechanisms throughout the last few decades. A brief classification of nanorobots is addressed below, depending on technological advancement, morphology characteristics, functional aspects, power supply, and biohybrid mechanisms. Ultimately, several cancer therapy, surgery, regenerative medicine, cell therapy, gene therapy and biomedical applications are reviewed. The field of nanorobotics has made significant progress. However, a number of concerns and challenges must be overcome before nanorobots may be used in patient care.

Key words: Nanorobots, Classification, Drug delivery, Gene therapy, Wound healing, Biomedical applications

1. INTRODUCTION

Drug delivery to targeted organs or tissues or cells is always challenging and interesting in the pharmaceutical research field. Conventional drug delivery methods not successful in direct delivery of a drug to targeted organs and achieving a maximum therapeutic effect with minimal side effects. In conventional drug delivery systems delivery of drugs depends upon the movement of body fluids to find their way around the body. Sometimes this type of delivery fails to treat some disease conditions like stroke and glioblastoma. Existing conventional drug delivery systems, delivers the drug directly into the systemic circulation to achieve maximum therapeutic effect. Conventional drug therapies unable to deliver the drugs more accurately to specified target tissues due to lack of navigational ability. Delivery of drugs to inaccessible tissue within the human body remains a challenge [1]. To achieve targeted delivery of therapeutic agents, the drug delivery system must possess autonomous propulsion and controlled navigation. To overcome all these challenges, a novel drug delivery system required. Nanorobotics is an emerging field that holds considerable promise for advanced diagnosis and treatment. This field has attracted tremendous interest among research groups due to their autonomous mobility and perform complex tasks at small scales. Nanorobots can evolve as a superb vision of medicine in the future. Nanorobots can fulfill all these requirements and able to serve as a promising strategy to solve all these challenges. An ideal nanorobot must possess defined target movement and autonomous drug delivery capabilities. As the nanorobot delivers the drug to a specific target site, it must be discharged from the body safely without causing toxic effects. Discharged nanorobots from the excretory channels of the body must be biodegradable and stable in external environment [2].

2. NANOROBOTS

Nanorobotics is the science which deals with robots at nanoscale. Nanorobots size usually ranges from 1 to 100 nanometers (nm). Nanorobots are specialized devices designed to perform a designated task. Nanorobots are miniaturized molecular nanomachines able to navigate autonomously in biological fluids with efficient cargo towing and penetrating abilities. Nanorobots are artificial, sophisticated submicron devices navigated by self propulsion or an externally controlled propulsion mechanism. Nanorobots are fabricated by assembling different components of miniaturized individual parts or integration of inorganic components with biological cells or molecules. Nanorobots are created from nanomaterials which will do the specified task. Nanomaterials are defined as materials with a diameter between 1 and 1000 nm. Nanomaterials from the past few decades have shown promising effects on drug delivery by passive or active targeting mechanisms [3]. Active targeting mostly depends on the over expression of receptor molecules, whereas passive targeting relies on the absorption of specific-sized nanomaterials by cancer tissues or lymph nodes. A nanorobot is an autonomic preprogrammed structure of atomic level [4]. The list of nanorobot examples is given in Table 1.

Table 1 Examples of Nanorobot with navigation mechanism

S.NO	Nanorobot	Navigation mechanism
1.	Helical Propeller	Magnetism
2.	Artificial bacterial flagellum	Magnestism
3.	Nanofish	Magnetism
4.	Two armed nanoswimmer	Magnetism
5.	2D Nanoswimmer	Magnetism
6.	Antibacterial nanorod	Ultrasound/Bioreceptors
7.	Tubular Nanorobot	Diffusion/bioreceptors
8.	DNA Walker	Bioreceptors
9.	Tetrahedron DNA	Diffusion/Bioreceptors
10.	Nanorod with flagellum tail	Acoustic waves/Magnetism
11.	V Shaped nanorod	Hydrogen peroxide decomposition

Nanorobots are nanoelectro mechanical systems having the properties of sensing, actuation, control, communications, powering and data transmission [5]. The various components of nanorobots includes micro camera, electrodes, lasers, ultrasonic signal generators, swimming tail and payload. Nanorobots are nanomachines connect the various interdisciplinary areas of nanotechnologies and nanoscience to solve real time challenges including targeted drug delivery. Nanorobots enhance the delivery of drugs and imaging contrast agents towards targeted sites due to their autonomous propulsion and improved navigation across biological fluids [6].

Nanorobots are functional molecular devices that are self assembled and propelled by external sources and can perform various tasks. These are programmed devices inserted through catheters or injected through blood vessels commanded by an outside surgeon will act as onsite surgeon in various complex vascular surgeries [7].

Most of the researches opted for intravenous route of administration as a portal of entry for nanorobots. Nanorobots after entering into the systemic circulation guided by magnetic fields and field gradients to reach the target site and finally activating them to promote the diffusion of drugs across the cell membranes of the targeted tissue. Nanorobots can utilize the endogenous fuels such as glucose, urea and adenosine -5- triphosphate (ATP) for navigation without the need of external equipment or actuation. While designing nanorobots it is important to design self-powered systems that are biocompatible, non-immunogenic and use fuel resources readily available in the body. Nanorobots behave swarm like devices could be useful in biomedicine for theranostic applications [8].

2.1. Classification of nanorobots

Nanorobots are generally classified based on morphology, function, propulsion mechanism and biohybrid mechanisms. Classification of nanorobots was given in Fig.1.

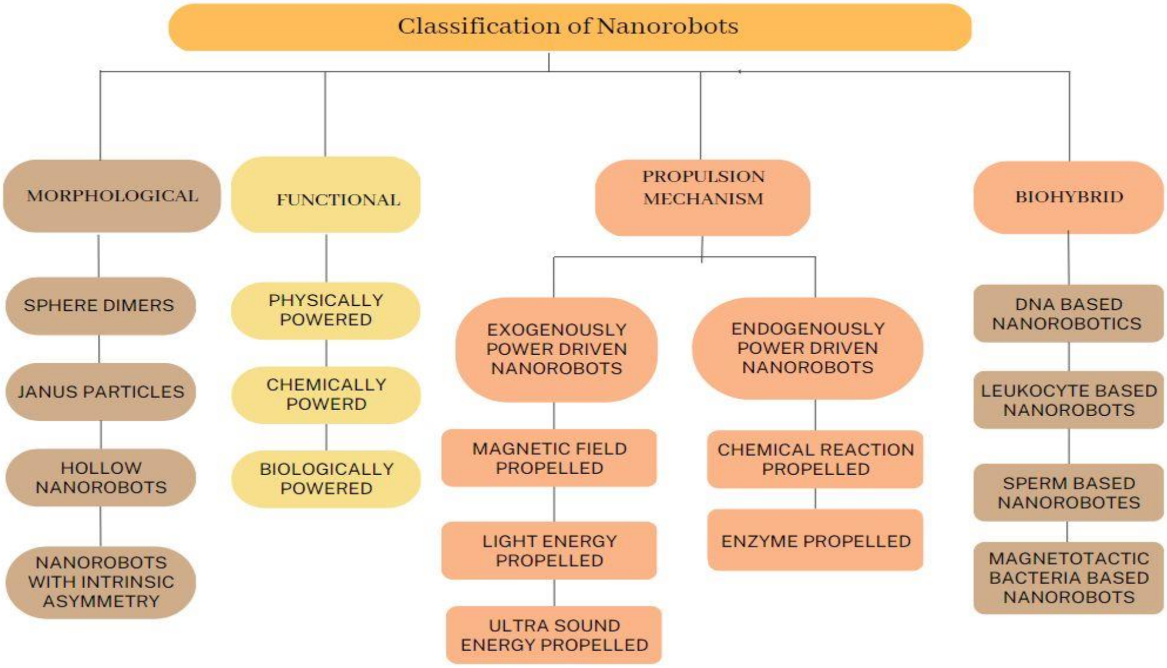

Fig.1. Classification of Nanorobots

2.1.1. Morphological classification

Morphologically, nanorobots are classified into four categories based on geometry and synthesis [9]. Morphological nanorobots was represented in Fig.2.

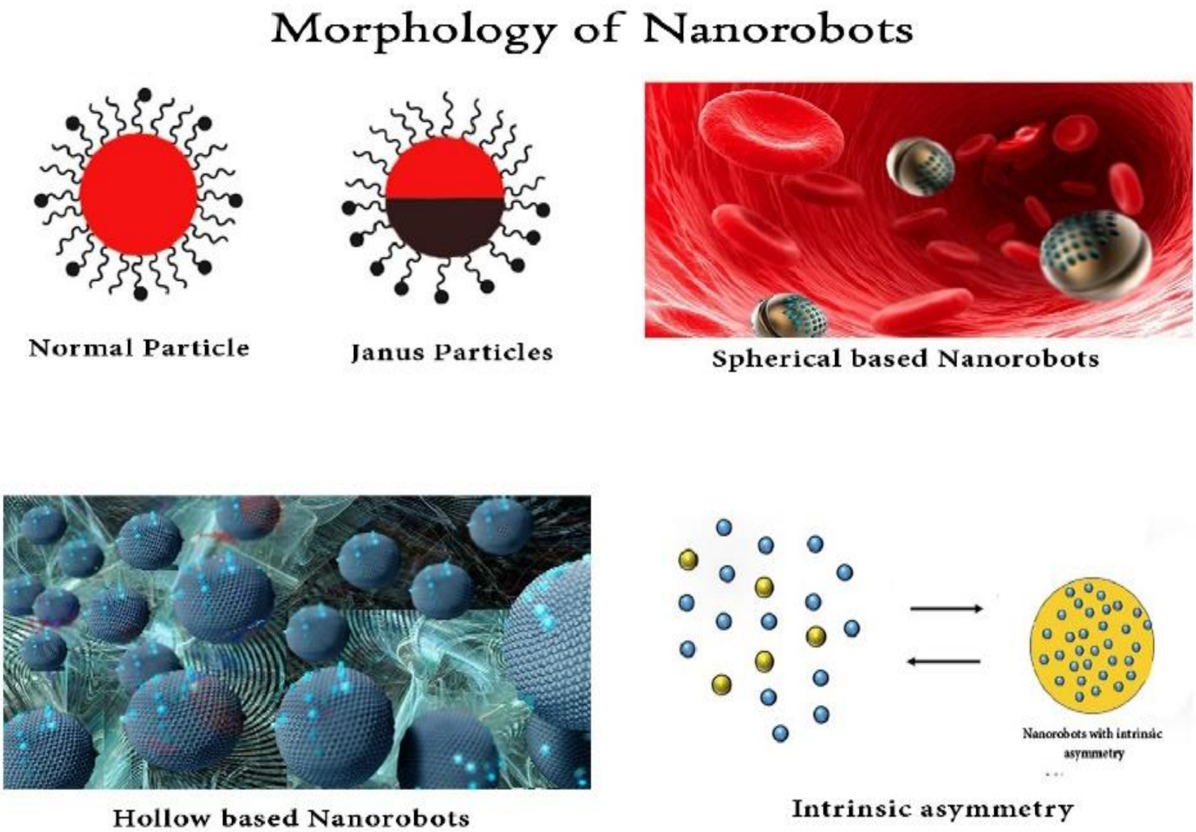

Fig.2. Morphology of Nanorobots

1) Sphere dimers
2) Janus particles
3) Hollow nanorobots
4) Nanorobots with intrinsic asymmetry

2.1.1.1. Sphere dimers

It consists of two halves. One half is made up of a silica sphere and the other half is made up of a platinum sphere. Both halves are made as a single unit by thermal annealing. Sphere dimers are fabricated by surface articulation of silica nanoparticles with platinum deposited on one side [10].

2.1.1.2. Janus particles

Janus particles are prepared by incorporating different metals in the form of layers on mesoporous silica nanoparticles. They can navigate due to the oxygen bubble generation. Oxygen bubbles generated due to decomposition of hydrogen peroxide by the platinum layer [11].

2.1.1.3. Hollow nanorobots

These are made by inserting catalyst in the hollow particles. It resembles a tubular rocket like structure with predetermined speed. Hollow nanorobots are prepared by advanced atomic layer deposition technique. This technique was used in creating 100 nm nano rockets. Hollow nanorobots are composed of platinum in the inner shell and titanium dioxide (TiO_2) as the outer shell [12].

2.1.1.4. Nanorobots with intrinsic asymmetry

Topological asymmetry used for self propulsion effects of nanorobots. Enzyme powered nanomotors shows enhanced diffusivity due to the inherent asymmetry of nanorobots.

2.1.2. Functional classification

Nanorobots are classified into three major groups based on their functioning [13].

1. Physically powered nanorobots utilize external energy sources such as magnetic fields, ultrasound or light fields for their navigation.
2. Chemically powered nanorobots utilize internal energy sources such as glucose, urea, hydrogen peroxide for their navigation.
3. Biohybrid systems integrate nonliving components with biological components such as motile organisms, which serve as the engine of the nanorobot and helps in navigation.

2.1.3. Propulsion mechanism based classification

Nanorobots are classified based on the propulsion mechanism and nature of power source. Propulsion based nanorobots was shown in Fig.3.

1. Exogenous power driven nanorobots
2. Endogenous power driven nanorobots

2.1.3.1. Exogenous power driven nanorobots

External power sources such as magnetic field, light energy, ultrasound energy is used in the drug delivery mechanisms. To design nanorobots with multiple functions, several driving forces and mechanisms are combined to achieve the targeted tasks [14,15].

1. **Magnetic field propelled nanorobots**

   Magnetic field has unique characteristics such as a strong driving force, navigation control and noninvasive to the human body. It is effectively used to propel nanorobots in non-contact manner and deliver the drugs at the targeted site.

2. **Light energy propelled nanorobots**

   Nanorobots are propelled by light irradiation or photo catalysis mechanisms. They initiate the conversion of light energy into mechanical energy, which leads to thermal and chemical reactions. Energy liberated during these reactions utilized for navigation of nanorobots.

3. **Ultrasound energy propelled nanorobots**

   Ultrasound has excellent penetrating ability, strong adjustability which propels the nanorobots towards the tumor cells and enhance the drug uptake by tumor cells.

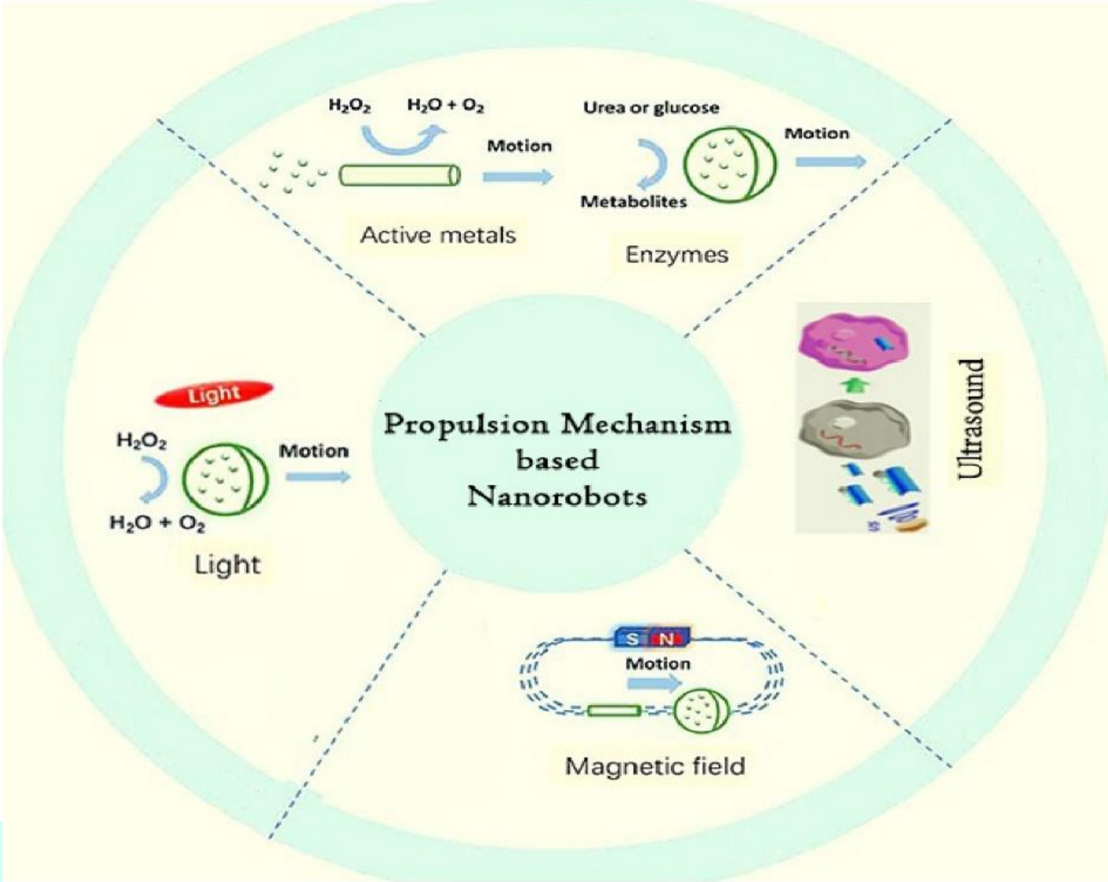

Fig.3. Propulsion mechanism based Nanorobots

2.1.3.2. Endogenous power driven nanorobots

In this case, nanorobots will utilize biological fuels as a power of source. Examples of biological fuels are Hydrogen peroxide, urea, glucose, adenosine-5- triphosphate (ATP). Endogenous power uses its own fuel to achieve autonomous navigation of nanorobots.

Chemical reaction propelled nanorobots

Hydrogen peroxide can be decomposed into water and oxygen in the presence of peroxidase enzyme, where the released oxygen bubbles will serve as a source to propel nanorobots.

Urea gets hydrolyzed in presence of urease enzyme. During hydrolysis, it is converted into ammonium ions and bicarbonate ions. Local electric filed can be created due to the faster diffusion of ammonium ions. This electric field helps in the diffusive motion of the particles. Glucose will be converted into D- glucono1,5 lactone and hydrogen peroxide in presence of glucose oxidase enzyme. Hydrogen peroxide can be used in association with enzymes such as catalase for powering nanorobots [16].

Enzyme propelled nanorobots

Enzymes involved in catalytic reactions generate oxygen bubbles, which act as a driving force for nanorobots. Oxidoreductase enzymes act as catalytic engines for nanorobots. Glucose oxidase enzyme involved in conversion of glucose to gluconic acid and hydrogen peroxide. Catalase enzyme involved in conversion of hydrogen peroxide to water and oxygen. This oxygen helps in the navigation of nanorobots. Urease an enzyme which involved in the conversion of urea into carbon dioxide and ammonia [17].

2.1.4. Biohybrid classification

Biohybrid nanorobots are small devices articulated from biological components such as (Deoxyribonucleic acid (DNA), enzyme, cytomembrane and cells) and artificial components such as (inorganic or polymer particles). They can perform multiple tasks such as single cell manipulation, cell microsurgery and targeted drug delivery [18]. Biohybrid nanorobots was shown in Fig.4.

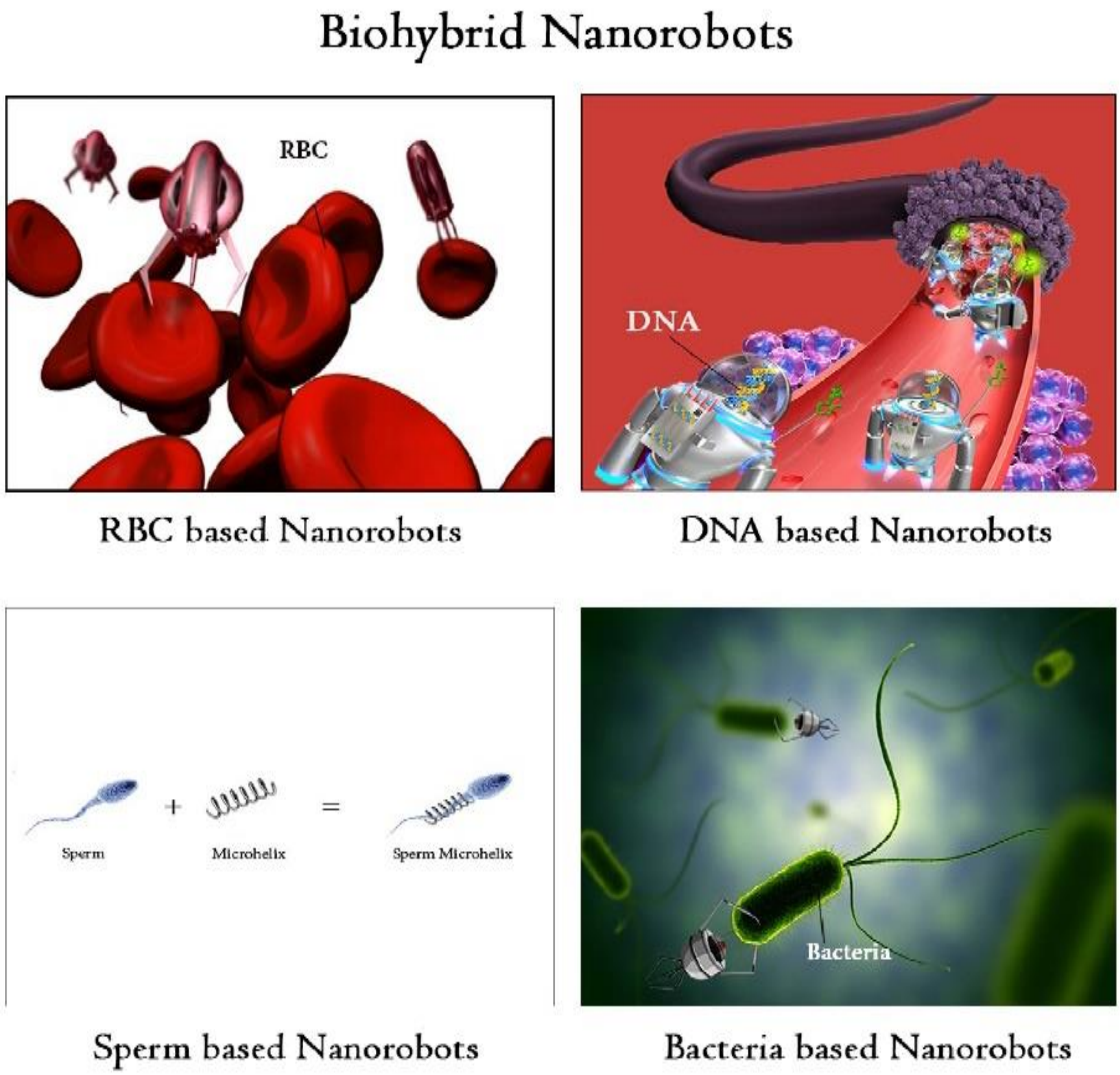

Fig.4. Biohybrid Nanorobots

2.1.4.1. DNA based nanorobots

DNA Origami is used to construct DNA nanorobots. In this technique, DNA nanostructures are obtained by repeated folding of single stranded DNA and fixing the structure with the help of oligonucleotides. Biohybrid magnetic microrobots are produced by attaching DNA flagella to magnetic iron oxide particles. They are useful in tumor targeted drug delivery and vaccination for precision cancer therapy [19].

2.1.4.2. Leukocyte based nanorobots

Macrophage based biohybrid nanorobots are called as immunobots which deliver anticancer drugs to tumors and useful in targeted immunotherapeutics. Neutrophil based biohybrid nanorobots are called as neutrobots which deliver drugs to malignant glioblastoma. The advantage of nanobots is they can escape the phagocytosis and removal by mononuclear phagocyte system [20].

2.1.4.3. Sperm based nanorobots

Male reproductive cells are called as sperms, and they have a tail known as flagellum. Motile sperms are converted to robotic micro swimmers called as spermbots. Sperm based drug delivery system can utilize rheotaxis and thigmotaxis of sperms to reach target site and release drugs [21].

2.1.4.4. Magnetotactic bacteria based nanorobot

Bacteria based biohybrid micro swimmers are called bacteriabots. Motile *E. Coli MG1655* is used for bio adhesion to epithelial cells and for targeted drug delivery towards the epithelial cells in urinary and gastrointestinal tracts. Bacteriabots are used for delivery of anticancer drugs like doxorubicin to the targeted site.

2.2. Objectives of nanorobots in biomedical applications and drug delivery [1-15]

1. Tunable physicochemical properties.
2. High surface area and volume for large drug payload and their controlled delivery.
3. Easy surface functionalization with targeting ligands and biomolecules.
4. Continuous monitoring of the body and giving feedback.
5. To destroy cancerous cells without affecting the healthy cells.
6. To repair tissues, clean blood vessels, airways and transform physiological capabilities.
7. To act as autonomous onsite surgeon inside the human body.
8. Able to carry large payload than a small molecule while retaining its smooth circulation throughout the blood stream.
9. Finding out the method of entry into the body for the nanorobot.
10. Propulsion mechanism of the nanorobot.
11. Control of the device.
12. Appropriate power source to nanorobot.
13. Locating substances to be eliminated by the nanorobot.
14. Continuous monitoring of the body and giving feedback.
15. Better accumulation and binding on specific sites owing to small dimensions.
16. Multifunctionality and modality for imaging and therapeutics.
17. Monitor the patient's body continuously and be able to detect cancer and other diseases at early stages.

2.3. Limitation of nanorobots [15-25]

1. Nanorobots aggregate with each other easily and creates problems inside the body.
2. Size variation is also a problem for entering of nanorobots into the cells and tumors.
3. Nonspecific biodistribution is also a major concern for the traversal of nanorobot inside the body.
4. Toxic effects and side effects may result due to long term retention of nanorobots inside the body.
5. Low accumulation of nanorobots in targeted tissue results in poor resolution.
6. Biohybrid nanorobots suffers with slow degradation.
7. Fabrication of nanorobots is a complex technology.
8. Surface modification of nanorobots is very difficult, while traversal of nanorobots inside the body.
9. Nanorobots locomotion in biological fluids very difficult and it depends on the nature of the material.
10. Biocompatibility or biodegradability nanorobots is very poor as the human body recognize the nanorobots as foreign particles.
11. The procedures adopted for diagnosis and treatment by nanorobots are time consuming.

2.4. Advantages of nanorobots [25-30]

1. Nanorobot drug delivery system enhances bioavailability.
2. Nanorobots reaches inaccessible areas in human anatomy which are not operatable at the surgeon's operating table.
3. Nanorobots carries the drug payloads and releases the drug molecules where ever needed.
4. Nanorobots can be controlled by external computer operation with nobs to fine tune the amount of drug released, frequency of dosing and time of release.

2.5. Disadvantages of nanorobots [30-37]

1. Design, components and construction cost of nanorobot is very high.
2. The technology used to design of nanorobot is highly sophisticated and complex in nature.
3. As the components and working mechanism of nanorobots are electric in nature, they are susceptible to electrical interference from external sources. They are highly influenced by RF or electric fields, EMP pulses and stray fields from other in vivo electrical devices.
4. Electrical systems can create stray fields which may activate bioelectric based molecular recognition systems in biology and may cause severe adverse effects at the cellular levels.

2.6. Design and fabrication of nanorobots

Nanorobot 3D prototyping can be achieved by a nanorobot control design software (NCD software). Nanorobot interactions inside the body can be estimated by NCD simulations. NCD is an advanced nano mechatronics simulator that provides physical and numerical information for nanorobot task based modeling. The nanorobot is designed in such a way that once it completes its task at the targeted site it comes out of the body through natural metabolism [22].

2.7. Nanorobots communication

Nanorobots communicate with one another by ring topography network. It requires three different forms of nanorobot.

1. A singular gateway that could communicate with the outside environment
2. An intelligent capsule moving inside the body and delivering the payload
3. A stationary nanorobot to hold the majority of the drug.

It will work by detecting any cellular changes, hormonal changes, antibody concentration changes and chemical changes inside the body. After detecting the changes, intelligent moving nanorobot moves to target site and precisely release its contents. The first nanorobot collects information and send this to other nanorobots using the intelligent travelling nanorobots. This ensures that shared information could be effectively transmitted throughout the body using a connected nanonetwork [23].

2.8. Mechanism of action

Nanorobots consists of proximity sensors sense both moving and nonmoving obstacles that hinder their path. Nanorobots moves in a predetermined path by checking the obstacles for every 0.5mm and select the shortest path for navigation. If any obstacles come in their pathway nanorobots wait for 0.0025 milli seconds and select new path for their traversal [24]. Nanorobots after reaching the target site, deliver drugs by utilizing internal and external sources. Once the target was achieved, they will be removed from the body through human excretory channels. In some cases, they can also remove by active scavenger systems, which are known as nanoterminators.

3. Applications of nanorobots

3.1. Nanorobots in cancer detection and treatment

Cancer can be curable if it is diagnosed at early stages. Nanorobots helps in the early diagnosis of cancer as the nano sensors can detect tumor producing cells at early stage [25]. Chemotherapy has side effects as existing anticancer drug delivery systems lack intrinsic navigation for long circulation time, targeting, localized drug delivery and tissue penetration [26]. As nanorobots have self navigational functions, precise cell targeting, tissue penetration and maximum therapeutic benefit can be achieved.

3.2. Nanorobots in surgery

Surgeons are constantly looking for alternative ways to treat the patients so that they will follow minimally invasive procedures during surgery, as recovery rate is faster when a lesser trauma is inflicted upon a patient. Due to minimum invasive procedures, there are usually few complications can be possible after the operation. The major objectives of nanorobots usage in surgery will be early detection, diagnosis, prevention or treatment of disease at the cellular or subcellular level [27]. Surgeons with the aid of surgical nanorobots perform operations with precision at nano, micro and macro scale dimensions. Micro syringes and catheters are used to introduce surgical nanorobots into the circulatory system of the human body. Surgical nanorobots act as a semi-autonomous onsite surgeon inside the human body and are programmed or directed by a human surgeon [28].

3.3. Nanorobots in diagnosis and testing

Nanorobots can be used for early disease identification at the cellular and molecular levels. Nanorobots helps to collect biological samples and tissue fluids to make multiple analyses at the micro level [29].

3.4. Nanorobots in gene therapy

Gene therapy has a potential that modifies a person’s genes to treat or cure genetic disorders. Gene therapy works by replacing a disease causing gene with a healthy copy of a gene or inactivating a disease causing gene that is not functioning properly, or introducing a new or modified gene into the body to treat a disease [30]. Nanorobots acts as a gene delivery system and deliver gene therapy at target sites. Nanorobots reaches target sites through blood circulation and penetrates tumor cells and turn off an abnormal gene. Nanorobots deliver genetic materials to target cells very easily due to their small size and their effective interaction with biomolecules at the cell surface.

3.5. Nanorobots in regenerative medicine and cell therapy

Regenerative medicine helps in regenerating human cells to restore normal function. Regenerative medicine therapies use of stem cells for tissue regeneration. Magnetically guided nanorobots act as a carrier system and deliver stem cells to targeted areas in the body [31]. These applications demonstrate that nanorobots play a significant role as targeted drug delivery systems and aid in regenerative medicine and cell therapy in the future.

3.6. Nanorobots in wound healing

Healing of chronic wounds on its own is very difficult. Epidermal growth factors play a significant role in healing of chronic wounds. Biological mechanisms fail to assist chronic wound healing due to defective healing mechanisms or low levels of coagulation factors. In such cases, nanorobots act as a carrier for growth factors and clotting factors and effective delivery of these factors at chronic wound site enhance rapid and effective wound healing. Nanorobots applied to promote blood clot dissolution. Thrombolytic agents can easily be delivered at target site with the help of nanorobots. In this case, to dissolve blood clot, magnetically actuated nanorobots loaded with tissue plasminogen activator are applied. The flow of blood drove the nanorobots towards the blood clot. Once nanorobots reach the target site, they were rotated by an external magnetic field. Their rotation generated local flow mixing which induces an increased interaction of the tissue plasminogen activator with blood clot interface, results in acceleration of thrombolysis [32].

3.7. Nanorobots in dentistry

Nanorobotic dentifrices were incorporated in dental preparations such as mouth wash or medicated paste or dental gels. They utilize specific motility mechanisms to penetrate sublingual surfaces and destroy pathogenic bacteria. Nanorobots enriched colloidal suspension will be instilled in to the affected area to induce anaesthesia in the gingival region of the patient. Colloidal suspension contains millions of analgesic dental robots that respond to input supplied by the dentist can induce anaesthesia effectively [33]. Nanorobots in contact with the surface of the crown or mucosa can reach the pulp and control nerve sensation and helps in painless tooth up righting as well as rapid tissue repair. After completion of treatment, they restore this sensation there by, providing the patient with anxiety free and needle less comfort. Nanorobots induced anaesthesia is fast acting and reversible, with no side effects or complications associated with its use. Nanorobots helps in reducing hypersensitivity by occluding the defective dental tubules with native materials and cure dental cavities permanently.

3.8. Nanorobots in neurosurgery

Treatment of cerebral aneurysms in the field of neurosurgery is highly challenging as it is associated with increased morbidity and mortality. Rupturing of aneurysm is usually leads to mortality of the patients within 24 hours. There are no cost effective guidelines for screening of patients with cerebral aneurysms. Nanorobots can serve the purpose of screening a new aneurysm or close monitoring of an identified aneurysm. Nanorobots aid in the early detection of tumors and ischemic changes [34].

Spinal cord injury and nerve damage is also an important aspect of neurosurgery, where the goal of therapy is optimizing and improving nerve reconnection outcomes. Restoring connectivity with transected axons is an integral step to the restoration of function. Axon surgery can be facilitated by the use of nanoknife and dielectrophoresis.

3.9. Nanorobots in haematology

Nanorobots have a wide array of applications in haematology. Respirocyte is an artificial mechanical red blood cell which is a nanorobot to perform three major functions while circulating through the blood stream. Firstly, it collects oxygen and diffuses throughout the blood stream. Secondly, collecting carbon dioxide from tissues and transfers into the lungs for exhalation. Thirdly it will help in energy production by metabolism of glucose and that energy is utilized for its own functions. Respirocyte is able to carry 236 times more oxygen per unit volume compared to red blood cells.

Clottocyte is an artificial mechanical platelet. Clottocyte is 2 microns in size with 0.8 nm mesh enriched with blood coagulation proteins. It helps in the improvement of physiological haemostasis process [35].

Microbivores are artificial phagocytes. They have larger binding sites on their external surface, so they can be able to trap various pathogens from HIV to *E. Coli*. Microbivores are 80 times more potential than physiological phagocytes and clears septicemia within hours.

Antimicrobial resistance is a major concern nowadays. So, nanorobotical abilities capable to battle with infections and helps to overcome antimicrobial resistance.

3.10. Nanorobots in vascular therapy

Nanorobots helpful in screening and monitoring chronic life threatening conditions such as brain aneurysms, unstable atherosclerotic lesions and lung cancers [36]. Nanorobots have potential applications in vascular therapy. The intravascular navigational ability of nanorobots makes them as better tools for continuous monitoring of tumors, diagnosis of vascular abnormalities and targeted drug delivery to cancers. Nanorobots have the capability to provide direct therapy to the targeted area, either mechanically or pharmacologically [37].

4. FUTURE OF NANOROBOTS

The field of nanorobotics was evolving greatly in the medical field, but to become as real word clinical applications it has to tackle and address various key challenges and issues. Material biocompatibility and degradation are two major characteristics must be considered, while manufacturing nanorobots to address in vivo safety issues. Once, the nanorobots overcome the challenges and enter in clinical practice as promising drug delivery system, it will affect the lives of millions of people in the world. So, it is necessary to consider the economic, social and ethical implications of the use of nanorobots.

5. CONCLUSION AND FUTURE PROSPECTS

This review paper gives an overview of nanorobots functioning mechanisms and its applications in drug delivery. This review also emphasizes on current trends of nanorobotics for therapy, surgery, diagnosis and medical imaging. Nanorobotics in future evolve as modern medicine and can improve the quality of life of individuals. Nanorobots are programmed to perform specific biological tasks. Nanorobots have potential applications across all fields of medicine. Nanorobots have the capability of expanding therapeutic alternatives and also able to improve the efficacy of existing treatments.

REFERENCES

1. Y. Saadeh, D. Vyas, Nanorobotic applications in medicine: Current proposals and designs. American journal of robotic surgery. 1(1) (2014) 4 – 11. https://doi.org/10.1166%2Fajrs.2014.1010
2. F. Soto, J. Wang, R. Ahmed, U. Demirci, Medical micro/nanorobots in precision medicine. Advanced Science News.7(21) (2020) 1-34. https://doi.org/10.1002%2Fadvs.202002203
3. R. Arvidsson, SF. Hansen, Environmental and health risks of nanorobots: an early review. Environ. Sci.: Nano. 7 (2020) 2875 - 2886. https://doi.org/10.1039/D0EN00570C
4. H. Zhou, CCM. Marinez, S. Pane, L. Zhang, M. Pumera, Magnetically driven micro and nanorobots. Chem. Rev. 121(8) (2021) 4999-5041. https://doi.org/10.1021/acs.chemrev.0c01234
5. M. Aggarwal, S. Kumar, 2022. The use of nanorobotics in the treatment therapy of cancer and its future aspects: A review. Cureus. 14(9): e 29366. https://doi:10.7759/cureus.29366
6. VA. Rahul, A brief review on nanorobots. SSRG-IJME. 4(8) (2017)15-20. https://doi.org/10.14445/23488360/IJME-V4I8P104
7. G. Giri, Y. Maddahi, K. Zareinia, A brief review on challenges in design and development of nanorobots for medical applications. Appl.Sci. 11(21) (2021) 2-23. https://doi.org/10.3390/app112110385
8. F. Soto, R. Chrostowski, Frontiers of medical micro/nanorobotics: in vivo applications and commercialization perspectives toward clinical uses. Frontiers in bioengineering and biotechnology. 6 (170) (2018) 1-12. https://doi.org/10.3389/fbioe.2018.00170
9. F. Novotny, H. Wang, M. Pumera, Nanorobots: Machines squeezed between molecular motors and micromotors. Chem. 6(4) (2020) 867-884. https://doi.org/10.1016/j.chempr.2019.12.028
10. LF. Valadares, Y.G. Tao, N.S. Zacharia, V. Kitaev, F. Galembeck, R. Karpal, G.A. Ozin Catalytic nanomotors: self-propelled sphere dimers. Small. 6 (2010) 565-572. https://doi: 10.1002/smll.200901976
11. M. Xuan, J. Shao, X. Lin, L. Dai, Q. He, Self–propelled janus mesoporous silica nanomotors with sub-100 nm diameters for drug encapsulation and delivery. Chem Phys Chem. 15(11) (2014) 2255-2260. https://doi: 10.1002/cphc.201402111
12. J. Li, W. Liu, J. Wang, I. Rozen, S. He, C. Chen, H.G. Kim, H.J. Lee, H.B. Lee, S.H. Kwon, T. Li, L. Li, J. Wang, Y. Mei, 2017. Nano confined atomic layer deposition of TiO2 / Pt nanotubes: toward ultrasmall highly efficient catalytic nanorockets. Adv.Funct. Mater.27 (24): 17000598. https://doi.org/10.1002/adfm.201770146
13. J. Li, B. Avila, W. Gao, L. Zhang, J. Wang, Micro/nanorobots for biomedicine: Delivery, surgery, sensing and detoxification. Sci Robot. 2(4) (2017) 1-20. https://doi:10.1126/scirobotics.aam 6431.
14. J. Yang, C. Zhang, X. Wang, W. Wang, N. Xi, L. Liu, Development of micro and nanorobotics: A review. Science China Technological Sciences. 62 (2019) 1-20. https://doi.org/10.1007/S11431-018-9339-8
15. S. Nain, NN. Sharma, Propulsion of an artificial nanoswimmer: a comprehensive review. Frontiers in life sciences.8(1) (2015) 2-17 https://doi.org/10.1080/21553769.2014.962103
16. J. Xie, Y. Jin, K. Fan, X. Yan, The prototypes of nanozyme-based nanorobots. Biophys Rep. 6(6) (2020) 223-244. https://doi.org/10.1007/s41048-020-00125-8
17. C. Sealy, Enzyme powered nanorobots behave like a swarm. Nanotoday. 38 (2021) 10116 https://doi.org/10.1126/scirobotics.abd2823.
18. J. Li, L. Dekanovsky, B. Khezri, B. Wu, H. Zhou, Z. Sofer, 2022. Bio hybrid micro-and nano robots for intelligent drug delivery. Cyborg and bionic systems. 9824057, 1-13. https://doi.org/10.34133/2022/9824057
19. R. Devasena Umai, P. Brindha Devi, R. Thiruchelvi, A review on DNA nanobots- A new technique for cancer treatment. Asian J Pharm Clin Res. 11(6) (2018) 61-64. http://dx.doi.org/10.22159/ajpcr.2018.v11i6.25015
20. Y. Hu, 2021. Self-assembly of DNA molecules: Towards DNA nanorobots for biomedical applications. Cyborg and bionic systems.9807520,1-3. https://doi.org/10.34133/2021/9807520
21. D. Wang, C. Gao, C. Zhou, Z. Lin, Q. He, 2020. Leukocyte membrane coated liquid metal nanoswimmers for actively targeted delivery and synergistic chemothermal therapy. Research. 3676954. https://doi.org/10.34133/2020/3676954
22. Z. Wang, Z. Xu, B. Zhu, Y. Zhang, J. Lin, Y. Wu, D. Wu, Design, fabrication and application of magnetically actuated micro/nanorobots: A review. Nanotechnology.33(15) (2022). https;//doi: 10.1088/1361-6528/ac43e6
23. N. Celi, D. Gong, J. Cai, 2021. Artificial flexible sperm like nanorobot based on self assembly and its bidirectional propulsion in precessing magnetic fields. Scientific reports.11, 21728. https://doi.org/10.1038/s41598-021-00902-6
24. K.K. Dey, X. Zhao, B.M. Tansi, W.J. Mendez-Ortiz, U.M. Cordova-Figueroa, R. Golestanian, A. Sen, (2015) Micromotors powered by enzyme catalysis. Nano Lett. 15(12) (2015) 8311-8315. https://doi.org/10.1021/acs.nanolett.5b03935
25. R. Maheswari, S. Sheeba Rani, V. Gomathy, P. Sharmila, Cancer detecting nanobot using positron emission tomography. Procedia computer science.133 (2018) 315-322. https://doi: 10.1016/j.procs.2018.07.039
26. N.J. Shetty, P. Swati, K. David, Nanorobots: Future in dentistry. 25(2) (2013) 49-52. http://dx.doi.org/10.1016/j.sdentj.2012.12.002
27. S.S. Andhari, D. R.D. Wavhale, K.D. Dhobale, B.V. Tawade, G.P. Chate, Y.N. Patil, J.J Khandare, S.S. Banerjee, Self-propelling targeted magneto nanobots for deep tumor penetration and pH responsive intracellular drug delivery. Scientific reports nature research. 10 (2020) (4703). https://doi.org/10.1038/s41598-020-61586-y
28. S. Mali, Nanotechnology for surgeons. Indian journal of surgery. 75(6) (2013) 485-492. https://doi:10.1007/s12262-012-0726-y
29. P. Sharma, Nanorobots in surgical applications. International journal of robotics and automation.4 (2) (2018) 1-10
30. Y. Zhang, Y. Zhang, Y. Han, X. Gong, Micro nanorobots for medical diagnosis and disease treatment. Micromachines 13(5) (2022) 648. https://doi.org/10.3390/mi13050648
31. A. Pedram, H.N. Pishkenari, Smart micro nanorobotic systems for gene delivery. Curr Gen Ther. 17(2) (2017) 73-79. https://doi.org/10.2174/1566523217666170511111000
32. Y. Feng, M. An, Y. Liu, MT. Sarwar, H. Yang, 2022. Advances in chemically powered micro/nanorobots for biological applications: A review. Advanced functional materials. https://doi.org/10.1002/adfm.202209883

33. R. Cheng, W. Huang, L. Huang, B. Yang, L. Mao, K. Jin, Acceleration of tissue plasminogen activator mediated thrombolysis by magnetically powered nanomotors. ACS Nano. (8) (2014) 7746 -7754. https://doi: 10.1021/nn5029955
34. Y. Kasimoglu, D. Tabakcilar, ZA. Guclu, SY. Nemoto, EB. Tuna, B. Ozen, T. Tuzuner, G. Ince, Nanomaterials and nanorobotics in dentistry: A review. Journal of Dentistry Indonesia. 27(2) (2020) 77- 84. https://doi: 10.14693/jdi. v27i2.1154
35. M. Sivasankar, RB. Durai raj, 2012. Brief review on nano robots in biomedical applications. Adv Robot Autom. https://doi: 10.4172/2168-9695.1000101
36. M.A. Zeeshan, K. Shou, K.M. Shivaram, T. Wuhrmann, S. Pane, E. Pellicer, B.J. Nelson, Nanorobotic drug delivery. Materials today. 14 (1-2) (2011) 54. https://doi: 10.1016/S1369-7021(11)70039-6
37. J. Rajesh, G. Pavithra, T.C. Manjunath, Design and development of nanobots for cancer cure applications in biomedical engineering. International Journal of Engineering Research & Technology. 6(3) (2018) 1-7. https://doi: 146031754