

INNOVATIONS IN NANOMEDICINE: USING NANOROBOTS TO REVOLUTIONISE CANCER THERAPIES

NANOTIPTA YENİLİKLER: KANSER TEDAVİLERİNDE DEVRİM YARATMAK İÇİN NANOROBOTLARIN KULLANILMASI

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ABSTRACT:

As computerization and AI have advanced, the healthcare industry, particularly the field of cancer research, has undergone a complete revolution. The combination of nanorobots and AI in healthcare is designed to enhance the delivery, diagnosis, and treatment of drugs. Unlike chemotherapy and radiation therapy, nanorobots delivers drugs precisely to the affected areas with fewer side effects and better results. Like, doxorubicin which is a powerful chemotherapy drug, could be enclosed in a nanorobot that moves on its own or controlled to precisely deliver the medication to the cancerous area.

Moreover, nanorobots can have a passive or active purpose, and different categories include Magnetic, enzyme based, bacterial, and AI-based nanorobots. Nevertheless, these systems encounter challenges related to biocompatibility, power supply, and real-time monitoring. These can be overcome by using, AI and machine learning, offer vital answers to enhance the self-navigating and decision making processes that support the use of nanorobots.

Overall, while there have been significant advancements in cancer treatment, there are still several issues that need to be resolved before utilizing nanorobots for improved and safer therapies for cancer patients in the future, to enhance their quality of life. This article will explore the different types of nanorobots, how

and why they are used including the use of doxorubicin and there future aspects.

Keywords: Nano-robots, Micro-carriers, Artificial Intelligence, Machine Learning, Neuro-Dynamic Programming, doxorubicin.

Chemical compounds –Doxorubicin (PubchemCID :31703)

ÖZET:

Bilgisayarlaşma ve yapay zeka ilerledikçe sağlık sektörü, özellikle de kanser araştırmaları alanı tam bir devrim geçirdi. Sağlık hizmetlerinde nanorobotların ve yapay zekanın birleşimi, ilaçların dağıtımını, teşhisini ve tedavisini geliştirmek için tasarlanmıştır. Kemoterapi ve radyasyon terapisinden farklı olarak nanorobotlar, ilaçları etkilenen bölgelere daha az yan etkiyle ve daha iyi sonuçlarla tam olarak ulaştırır. Mesela güçlü bir kemoterapi ilacı olan doksorubisin, kendi başına hareket eden bir nanorobotun içine yerleştirilebilir veya ilacın kanserli bölgeye hassas bir şekilde iletilmesi için kontrol edilebilir.

Dahası, nanorobotların pasif veya aktif bir amacı olabilir ve farklı kategoriler arasında Manyetik, enzim bazlı, bakteriyel ve yapay zeka bazlı nanorobotlar bulunur. Bununla birlikte, bu sistemler biyouyumluluk, güç kaynağı ve gerçek zamanlı izleme ile ilgili zorluklarla karşılaşmaktadır. Yapay zeka ve makine öğrenimi kullanılarak bunların üstesinden gelinebilir; nanorobotların kullanımını destekleyen kendi

kendine gezinme ve karar verme süreçlerini geliştirmek için hayati cevaplar sunar.

Genel olarak, kanser tedavisinde önemli ilerlemeler kaydedilmiş olsa da, gelecekte kanser hastalarına yönelik daha iyi ve daha güvenli tedaviler sağlamak ve yaşam kalitelerini artırmak için nanorobotları kullanmadan önce çözülmesi gereken birkaç sorun var. Bu makale, farklı nanorobot türlerini, bunların nasıl ve neden kullanıldığını, doksorubisin kullanımı ve gelecekteki yönlerini inceleyecektir.

Anahtar Kelimeler: Nano robotlar, Mikro taşıyıcılar, Yapay Zeka, Makine Öğrenimi, Nöro-Dinamik Programlama, doksorubisin.

Kimyasal bileşikler: Doksorubisin (PubchemCID :31703)

INTRODUCTION

The evolution of computers has been remarkable, progressing from devices the size of spacecraft to portable units that can be held in one's hand. These advancements have led to increased processing speed and capabilities that surpass human capacity, enabling further exploration and discovery.

In the contemporary era, computers and Artificial Intelligence (AI) have become integral to various fields and industries, including medicine. These technologies are utilized in treatments, diagnoses, surgeries, research, and pre-clinical studies of pharmaceuticals, reducing the need for animal testing. Computers and AI have demonstrated particular efficacy in cancer treatment, diagnosis, and tumor cell studies, providing enhanced accuracy, precision, and predictive capabilities for morphology and variants.

Cancer remains a leading cause of mortality in the present day. While chemotherapy and radiotherapy (Ceylan,2019; Shi,2020) can be effective in prevention and treatment, they often result in chronic side effects that may be more severe than the cancer itself, potentially leading to fatality. To address this issue, a novel drug delivery system utilizing (Singh,2023) nanorobots has been developed. These nanorobots possess (Wei,2020) pH and enzyme reflexes, similar to human bodily reflexes, enabling targeted drug delivery, sustained release, and improved drug efficiency in terms of accuracy and precision. This drug delivery system aims to minimize side effects and reduce cancer-related mortality rates. Over the past five years,

fish-shaped microbots and shape-morphing crab microbots (Xin ,2021) have been evaluated for use in cancer treatment. These designs are typically controlled by external stimuli such as magnets or magnetic actuation systems. Recent advancements have led to the development of self-driven nanorobots that respond to specific enzyme reflexes, addressing limitations of previous designs.

Doxorubicin, one of the most effective chemotherapeutic agents, has demonstrated high compatibility with nanorobots. However, it is associated with significant side effects, including dose-dependent toxicity. The conversion of doxorubicin into nanoparticles for delivery via nanorobots has shown potential in reducing toxicity and increasing efficacy. This approach also aids in overcoming pharmacokinetic resistance. The delivery of doxorubicin through nanorobots represents a targeted delivery method for cancer cells. Doxorubicin's mechanism of action involves inducing cell death through multiple pathways, including intracellular interactions, reactive oxygen species generation, and apoptosis induction via DNA-adducted configurations and histone eviction. This text will examine the delivery of doxorubicin through nanorobots.

Why Nanorobots in cancer treatment.....?

Nanorobotics and nanomedicines represent novel drug delivery systems in cancer treatment history when compared to chemotherapy, radiotherapy, surgeries, and other therapies. In chemotherapy, drugs are administered through oral and intravenous routes. After administration, the drug travels throughout the body via systemic circulation, potentially causing blood toxicity, cell toxicity, liver toxicity, and other side effects. Consequently, the cure of cancer becomes secondary as the patient experiences these severe side effects caused by chemotherapy.

Radiotherapy generally utilizes X-rays, which include high-intensity electromagnetic radiation. While this causes tumor cell death, exposure to this radiation also affects surrounding cells, leading to their death. This treatment is not recommended for individuals aged between 10-12 years and less than 10 years.

Surgery may cure without side effects or with acute side effects, but in some areas, if the cell mass is removed, it cannot be regenerated. For example, if a tumor cell is located in the hand region and is removed by surgery, the excised cell mass may contain neurons that cannot regenerate,

resulting in the patient losing sensation in that particular area.

In the case of nanorobots and nanomedicines, the drug is delivered in a sustainable manner and in controlled dosages to mitigate the side effects present in other therapies. Side effects may still occur, but they depend on posological factors and patient compatibility.

Advantages:

- The drug is delivered to the targeted site, thus falling under the category of targeted drug delivery.
- No release of drug in systemic circulation prevents toxicity.
- The nanorobots can cross biological barriers present in the body (with exceptions - not all barriers).
- Can be administered orally or by infusions.

Disadvantages:

- Cost-intensive.
- Side effects (acute).

Targeting drug delivery systems for tumor therapy:

Passively targeted drug delivery systems:

The term "passive targeted drug delivery" is self-explanatory. It indicates that a nanorobot or microcarrier remains continuously active within the biological environment, prepared to respond to specific conditions and release medication at the intended location (Talebloo,2020).

For Example and consideration: Consider a video game character with passive abilities that are constantly active and display their effects when any attack occurs. The effectiveness of this drug delivery system is contingent upon both the properties of the tumor cells and the attributes of the material selected for microcarrier fabrication. Typically, materials that are prone to reaction are utilized in the fabrication process (Sato,2016).

The tumor exhibits the following characteristics:

- Extensive angiogenesis.
- Greatly increased production of permeability mediators.
- Irregular vasculature that has poorly aligned endothelial cells.
- Diminished functional receptors of angiotensin II.
- Diminished lymphatic system, and lacks smooth muscle layer.

Researchers observed this unique tumor features and made effective in Passive Targeted Drug Delivery Systems(PTDDS).

Active targeted Drug Delivery Systems:

Active targeted drug delivery the name itself indicates that the nanorobot or microcarrier is activated by any physiological or chemical factors that are present in the biological environment (Wang,2018, Kumari 2016).

Example and consideration:

Consider, for instance, a video game character with active abilities that the player can trigger during combat.

Similarly, these drug delivery systems and their advancements are utilized in controlling the nanorobot's movement, drug-carrying capacity, and release mechanisms. The microcarrier or nanobot can achieve sustained or complete drug release when exposed to specific organ conditions such as pH levels, light, acoustic waves, or ultrasound, Magnetic field, etc... The active and passive targeted systems are shown in figure-1.

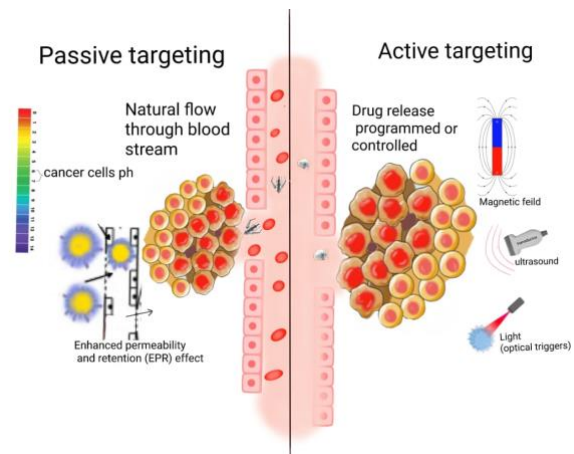


Figure 1- Active and passive targeting.

Different types of nanorobots:

Micro/Nanorobots:

MNRs-Medicinal Nano Robots can be (Alapan, 2020) self-propelled by converting the surrounding energy into the locomotion, thus breaking the factors of Brownian movement and low Reynold's number conditions. The propulsive force can be helpful to cross the Biological barriers like BBB-Blood Brain Barrier (Alapan, 2020, Zhang,2021), Dense Extracellular Barrier and most importantly Blood Tumour Barrier.

From the last decade researchers demonstrated (Zhou,2021) that the micro robots potentiality against cancer cells and the ability of delivery of drugs directly to cancer cells then followed by the advancements, with significant progress in recent years.

External-field-powered micro/Nanorobots:

The microbots are referred as fuel-free carriers that are Actuated by light, Electric field, (Hu,2021) Magnetic field and Ultrasound. Figure-2.

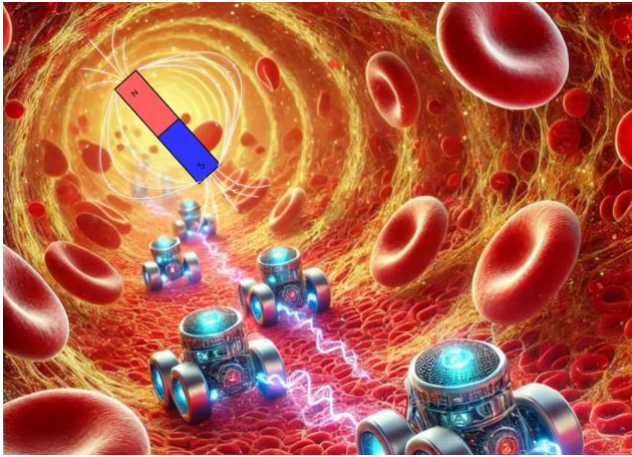


Figure 2-Magnetic guided nanorobots (in-vivo control of nanobots to the specific sight).

Compared with chemically-powered MNRs, external-field-powered MNRs have the advantages of better controllability, and less harmful undesired impact, so they have a broader application prospect.

(Wang,2021; Xin,2021) Magnetic driven MNRs are actuated by alternating Magnetic fields like rotating, oscilating, and Interrupted magnetic field. Generally magnetic MNRs are driven in Two ways they are(Xu, 2019).

- Magnetic MNRs move in low Reynold's number liquids by deforming their bodies when exposed to a rotating and oscillating magnetic fields.
- Magnetic fields can propel MNRs by producing an uneven force field in the surrounding area, as MNRs experience more notable hydrodynamic drag near the wall surface than the side further away from it.

These we can say like advantages. (Zang,2018)

Ultrasound is the biocompatible and powerful energy source which can be easily used by hospitals and laboratories. Generally, the interdigital transducers and acoustic wave devices can generate ultrasound standing waves (Zang,2022). When the microrobots are exposed to ultrasound field the MNRs experience the acoustic radiation forces which consists of primary radiation forces, the leading forces of this field responsible for delocalization of microrobots and the secondary radiation force is responsible

for the repulsion and attraction between each micro robots it is a weaker force. The first mechanism is called as self-acoustophoresis (Sun,2020).

The release of drug depends upon the pH at normal cells and the pH at the cancer cells(Shi,2020; Xin,2021). The pH also a factor and a characteristic feature to trigger either passive or active durg delivery systems which are acuated by magnetic field and ultra sound (Ceylan,2019).

Enzyme-Powered micro/nanorobots:

Enzyme-powered MNRs relay on biocatalytic reactions of widely available biocompatible fuel substrates. Therefore, they can also be actuated (Ren,2022)by biocompatible bioavailable fuels, like urease, glucose, and lipase, and are considered to be promising drug-delivery platforms for tumor therapy.

Example illustration:

Platelets play the most important role in human body we can target them by their receptors expressed on the surface. This will help the MNRs novel attempt. Therefore, researchers demonstrated the endogenous enzyme powered Janus platelet micromotor (JPL-Motor) system(Zhou ,2021). The Janus distribution of urease over the platelet surface results in the asymmetric biocatalytic decomposition of urea into ammonia and carbon dioxide. Subsequently, a concentration gradient and active directional flow of reaction products around JPL-motors are generated, which drives the JPL-motor to undergo self-diffusiophoretic propulsion. They demonstrated that the JPL-motor could achieve self-propulsion in the presence of urease, specifically target cancer cells and bacteria, and improve the anti-cancer and bacteria efficacy.

Light Driven Micro/Nanorobots:

The light sources used are (Liu,2021; Wang ,2021):

- Visible light (Bozoyuk, 2018)
- Near-infrared irradiation (Wang, 2018)

The light source aslo can be used as motion switch (Wei 2020, Wang 2018), and drug release stimulant. At proper irradiation time. Additional advantages of the light propelled microrobots are:

- Selective targeting.
- Immunity (Liu,2020)
- Tissue penetration.

Light-propelled MNRs can carry out the on-demand mission with minimal takeover.

The light field can also be used to induce surge behaviour in Microrobots. Figure 3.

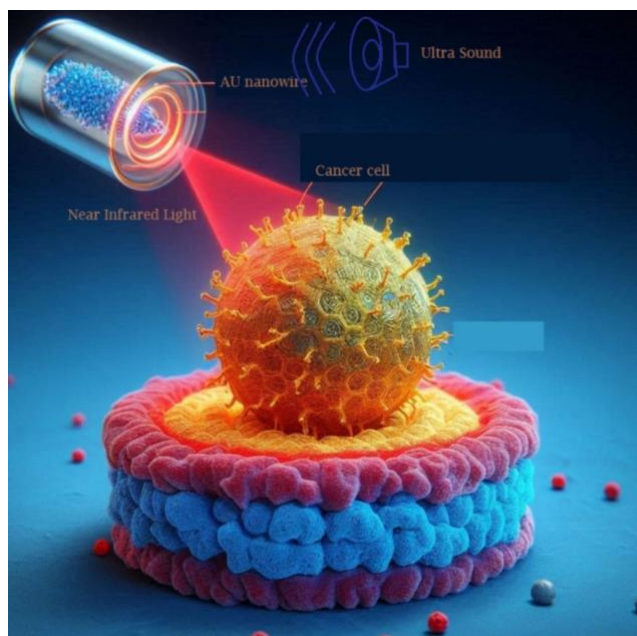


Figure 3- Light driven nanorobots (light source working as motion switch and drug release stimulant.

Bacterial microrobots:

Bacterial Biohybrids (Sato,2018) are the bacterial carriers and also biohybrids are called as a combination of non-living and living matter which carries the micro and nano-scale materials, (Talebloo,2020) which can transport the payload to the targeted sites under magnetic control, NIR- (Near Infrared irradiation) (Wang,2018)]. These are the novel approaches in drug delivery systems where a micro/nano scale mechanical devices are cannot be manufactured (Gao,2021) in less time but we can use bacterial biohybrids as carriers in targeted drug delivery. The name itself contains information that is (Wan,2019) Bio meaning “living organism” Hybrid meaning “bacteria changed from parasite to helper or combination of living and non-living”. This can be seen in figure-4. magnetic nanoparticles and nanoliposomes are loaded into this and therapy is initiated. In this process a specific strain of bacteria is used to utilize it.

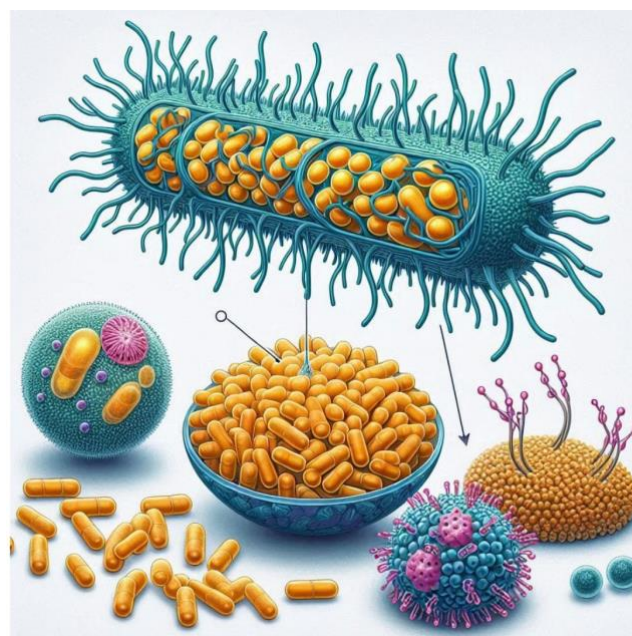


Figure 4-Bacterial nanorobots made from living (bacteria) and non-living materials used to deliver drugs to the targeted site.

This shows advantages like -

- Self propulsion without fuel consumption.
- Tissue penetration.
- Payload efficiency.

Why magnetic rays, Ultrasound and radiance fields.....?

Magnetic Resonance Imaging (MRI) is a diagnostic instrument that utilizes high-intensity magnetic fields to examine the human body for medical purposes. Ultrasound employs acoustic waves transmitted into the body, while near-infrared (NIR) light is involved in radiance fields. Ultrasound and magnetic fields are employed in the diagnosis of certain diseases and in fetal examinations, as well as for pregnant patients, due to their minimal harm to the human body and reduced likelihood of damaging cells and organ systems. Consequently, magnetic, ultrasound, and light-driven microrobots are utilized in cancer treatment. For experimental purposes, magnetic actuators, including permanent magnets, are used to drive microrobots, with observations conducted under a Transmission Electron Microscope (TEM).

In the context of patient treatment, permanent magnets are positioned around the patient to control microrobots in vivo. In vivo techniques involve placing ultrasound transducers around the patient and operating them to generate acoustic waves that propel the robots. The radiance field may serve as an active drug delivery system or a delocalizing stimulator for nanorobots.

Table 1-Different types of drugs used in various nanobots examples

Type	Example	Drug used	Other tasks	Advantages
Light:	- Azobenzene-coated polymer nanoparticles. - Janus SiO_2 Nanoparticles. TiO_2 Nanoparticles.	- Dofetilide. - Nile red. - Curcumin. - Doxorubicin. - Paclitaxel. 6-Mercaptopurine. - Curcumin. - Camptothecin. - Doxorubicin. - Imatinib. - Norflaxacin & Fenoxiam. - DEX. 5-Fluorouracil. - Cisplatin. - Paclitaxel.	- Monitoring in - Used minimally invasive surgeries. - Diagnosis.	- Clean energy. - Autonomic. - Small size range. - Less cost expensive. (Wan,2017 ;Mura2013; Key 2007,Xue 2016)
Magnetic:	Surface Walkers: - Janus Micro dimmer Surface Walker. - Rotating Nanowires. - Colloidal Microswarms. - Pine-pollen based micromotor. Flexible swimmers: - Nickel head & silver tail swimmer. - Sperm-shaped swimmer. Helical Swimmer: - Helical swimmer. - Rigid Helical Swimmer.	- Doxorubicin - Hydrochloride. - GAPDH siRNA. - MTX- Methotrexate Sodium	- Sensing. - Used in minimally invasive surgery. - Cell manipulations	- Precise. - Penetration. - Fuel free. - Reusable. - Better penetration among tissues. - Programmable. - Harmless to the patient. - Speed is negligible. (Zheng,2023;Sing,2010;Dreyfus 2005,Pak,2011)
Ultrasound:	- Au-Ru bimetallic Nanorods. - Microtubes. - RBC Microrobot.	- Doxorubicin. - Cisplatin. - Doxorubicin. - Pirfenidone. - Clodronate. - Camptothecin.	- Diagnosis. - Good Efficiency. - Speed in target reaching.	- Tunable. - Penetration. - Versatile. - Potential. (Villa 2019;Go 2020;Xu,2017; Kagan,2017;Wu,2014)
Motile Bacterial Biohybrids.	E.coli biohybrid based microrobot.	- Doxorubicin. - CFX(ciprofloxacin).	–	- Self propulsion. - Self repair. - Surgical Assistance. - Diagnosis. - Versatile. - Cell Manipulation. - Tissue Engineering. (Stanton 2016)

Note: Ciprofloxacin is not used as a main treatment. It is used as an add-on treatment, for infections caused by cancer cells in body.

Distinguish Characteristics of Liposomes:

Not able to perform additional tasks.

No Self Mobility moves based on systemic circulation.

Should be stored in stable environment.

Problem of accumulation on non cancerous tissues.

The above characteristics are mentioned in table are not performed by liposomes when compared to nanorobots.

Table 2-Difference between Liposomes and Nanorobots:

Table 2-Difference between Liposomes and Nanorobots:

Liposomes	Advanced Drug Delivery Systems (Nanorobots)
Structure: - Liposomes are spherical vesicles composed of phospholipid bilayer, often hydrophilic or lipophilic molecules, in their core. - They are biodegradable, biocompatible and simple. - They can evade immune systems due to above factors. - The size ranges from 50nm to several microns. (Zbilska, 2024; Liposomal Particles) Mechanism Of Action: - Liposomes follow passive condition in the body for drug release. - This systems works by encapsulating drug in it. (Liposomal Particles) Efficiency in delivery: - Liposomes shows high effective property improving the pharmacokinetics of drugs reducing systemic toxicity. - But shows slower process of drug release and its not precisely controlled. (Basu,2024;Chen 2024) Targeting Specificity: - Sometimes liposomes may not be always perfect in their targeting accuracy. - There is a chance of accumulation of liposomes on Non-Cancerous tissues it is un necessary (Chen, 2024;Eu J Phar Sci).	Structure: - Nanorobots are molecular machines at Nanoscale, composed of synthetic polymers, DNA & RNA strands and other nanomaterials. - There are more complex in their structures because of their synthetic and semi-synthetic nature and have functionalities like motors, sensors & responsive parts. - The size ranges from 1nm to 100nm. (Naik,2024) Mechanism Of Action: - Nanorobots shows sensitive mechanisms, where moving to specific sites in responsive to external stimulus. - They shows active targeted drug delivery and precision in drug delivery and they can perform controlled manner of drug release. - Sometimes they seek signals from the cancerous environment. (Basu,2024; Karthigai 2024) Efficiency in delivery: - Nanorobots shows more precise control over drug release imparts more efficient and on demand treatment. - They directly interact with cancer cells and provide control drug release, potentiality, and more effective drug delivery when compared to liposomes. - They can change according to programming of external stimuli, can also monitor drug's action, can perform real time adjustments to improve treatment outcomes. (Sahejwani 2024, Mukherjee 2024) Targeting Specificity: - Nanorobots shows Accurate Target identification and identification of cancer environment. - There is a communication between nanorobot to nanorobot and communication between nanorobot to technician and to physician (Sahejwani 2024).

Advanced Drug Delivery Systems (Nanorobots):

Pros:

- Accuracy in targeting cancer cells (Karthigai 2024, Soni 2024).

- Communication between nanorobots itself and between nanorobot to technicians (Sahejwani 2024).
- Controlled and potential release of drugs leads to minimize side effects (Soni, 2024).
- Less or no systemic toxicity and body toxicity (Sahejwani 2024).
- Excretion unchanged form.
- Used in various types of cancers and in minimal invasive surgery (Mukherjee, 2024).
- Nanorobots can perform other tasks like Diagnosis, Drug action monitoring, Real time tumor identification.
- Drugs can be carried by less number-means due to control release there is less consumption of nanocarriers and can prevent excess load of drug.

Cons:

- Cost expensive-even chemotherapy is also cost expensive.
- Time consuming for manufacture.
- Sophisticated manufacturing-includes engineering.
- Not obtained planned yield-loss of +/-15-25%.

Knowing about doxorubicin –

Introducing doxorubicin

Doxorubicin or Adriamycin is an anthracycline drug. It is one of the most used chemotherapeutic drugs for treating various Cancers Since its approval from FDA in 1974 (Punia, 2011). This is extracted from the bacterium *Streptomyces peucetius*. (Dai, 2016; Wicki 2015). Recommended mostly as an anti-neoplastic agent for treating malignancies (Wicki, 2015). This acts on in different ways by inducing cell death by reactive oxygen species generation (ROS) by free radical generation (Punia, 2021; Wicki, 2015). By DNA-adduct formation – intercalating with DNA leading to DNA strand breakdown causing cancer cell apoptosis. (Dai, 2016). Also by antineoplastic effect by topoisomerase II enzyme inhibition. (Punia 2021; Wicki 2015). Most recent find is that it leads to Chromatin damage through histone eviction from select Sites in genome (Punia, 2021; Sritharan, 2021).

Doxorubicin dark side-

Although it is an effective anticancer agent, it has many serious side effects such as cardiotoxicity, neuropathy, hepatotoxicity, nephrotoxicity, alopecia, typhoid, prevention of myelocytopenia, neutropenia, anaemia, thrombocytopenia, nausea

and diarrhea, due to lack of cancer. Found that cancer cells have gonadotoxicity. Anthracycline-induced cardiotoxicity is dose-dependent and may be fatal. Therefore, treatment should be stopped when the maximum tolerated dose is reached. Even patients with poor heart function are excluded from chemotherapy regimens containing anthracyclines. In addition to treatment-limited cardiotoxicity, treatment-related adverse events and gonadotoxicity are associated with anthracycline therapy (Sritharan, 2021).

How to overcome the dark side –

Chemotherapy drugs such as DOX, paclitaxel, camptothecin, etc. Are not specific for cancer cells and cause off-target damage. It is very beneficial in cancer treatment (Hamad,2023). Nanoformulations of doxorubicin are also approved by the FDA for medical use: Doxil for the treatment of Kaposi's disease, ovarian cancer, breast cancer and multiple myeloma (with Velcade), Myocet for breast cancer (with cyclophosphamide). Lipodox for breast and ovarian cancer (Punai 2021). The different types and formulation of nanorobots is given in Table 1.

Why doxorubicin is used and it's advantages

Doxorubicin (DOX), a potent and extensively utilized anticancer medication, is renowned for its capacity to eliminate malignant cells. Its integration with nanomedicine and nanorobotic platforms mitigates the constraints of traditional chemotherapy agents while boosting their efficacy. The process involves:

Precision and regulated administration: Nanotechnology, including nanoconjugates, nanomotors, and nanorobots, facilitates the accurate delivery of DOX to cancer cells. These mechanisms often react to specific tumor cues, such as acidic environments, ensuring targeted drug release and minimizing harm to healthy tissues.

Minimized adverse reactions: By restricting drug activity to tumor locations, these sophisticated systems substantially decrease systemic exposure and adherence, addressing a significant challenge associated with conventional chemotherapy agents. (Dai 2016; Wicki ,2015).

Enhanced immune response: DOX not only destroys cancer cells but also invigorates the immune system by increasing tumor antigens, bolstering the body's innate defenses against diseases. (Dai,2016; Sritharan, 2021).

Increased effectiveness: Nanotechnologies amplify DOX's therapeutic potential by enhancing drug delivery efficiency, retention at tumor sites, and synergistic effects like inducing apoptosis through reactive oxygen species (ROS) production.

Innovative therapies: Biological agents such as galactomannan and calcium peroxide, along with DNA nanotechnology, magnetic actuation, and aptamer targeting, represent advancements in the expanding interdisciplinary field of cancer treatment strategies.[56,57]

Disadvantages

1.Toxicity: It causes severe aspect effects, including cardiotoxicity and myelosuppression, which can persist inspite of nanocarrier structures.

2.Drug Resistance: Cancer cells often broaden resistance because of mechanisms like drug efflux and target changes.

3.Non-particular Targeting: Achieving specific focused on to cancer cells remains difficult, main to off-target consequences on healthful tissues.

4.Formulation Challenges: Developing strong and green nanocarriers, inclusive of SPIONs and micelles, is complicated and luxurious, with potential variability in drug launch and efficacy.

5.Regulatory and Biocompatibility Issues: Nanomedicine systems face regulatory hurdles and risks like immune responses or incomplete drug release.

The primary disadvantages of using doxorubicin in nanobots include dose-dependent toxicity, particularly myelosuppression and cardiotoxicity, as well as the emergence of multidrug resistance (Prados, 2012). These limitations restrict clinical use and effectiveness. Additionally, doxorubicin has low specificity against cancer cells, which can lead to unintended damage to healthy tissues (Prados,2012) (Dai 2016; Yijie 2024;Yanfang,2023).

Interestingly, while nanobots aim to improve drug delivery, they face their own set of challenges. These include difficulties in physicochemical characterization, large-scale reproduction, and potential toxicity profiles of the nanoparticles themselves (Panda, 2022). Furthermore, nanobot stability in biological fluids and overcoming barriers in the tumor microenvironment remain significant hurdles.

Other drugs used and their clinical trial phase

- Doxorubicin is typically combined with iron oxide nanoparticles and carbon nanotubes for optimize function. Phase 2.

- Paclitaxel will be well delivered into the blood system of a patient by an application of a nanoparticle carrier to improve its efficacy, as well as minimize side effects. Phase 1
- Cisplatin-This compound is further encapsulated into nanoparticles to achieve a more effective targeting of cancer cells. Phase 2.
- Gemcitabine: Nanoparticle formulations are more effective in the delivery of drugs to tumor sites. Phase 1.
- Camptothecin: Nanocarrier-assisted delivery enhanced by means of nano vessels also improved index of therapy. Phase 1.
- Docetaxel: Incorporation of nanoparticles into the systemic application will reduce their toxicity to improve targeting. Phase 2.
- Epirubicin-nanoparticle formulation for improved drug delivery and reduced side effects. Phase 1.
- Vinorelbine: With nanocarriers, it has been delivered to make it more potent and less toxic. Phase 1.
- 5-Fluorouracil: Used to enhance drug delivery to tumor sites. Phase 2.[Stadlbauer,2022, 79,61]

Note: Currently there are no licensed drugs in nanobort form but there are promising achievements in preclinical studies but not at approved by FDA.

In all over the world there is no proper evidence for fully functioning Nanorobots among the biological environments of human body there are still undergoing the research works and trails on animal models and cell lines of human body. According to the trails(Pre-Clinical Trails)till now as follows :

In-vivo studies of some medicinal Nanorobots On Animal models and Cell lines of human beings:

I.Gold Nanorobots Loaded with Doxorubicin:

Principle: Doxorubicin is a potent chemotherapeutic agent that is used in various types of cancer treatments which can directly binds to DNA and blocks the enzyme Topoisomerase II which is responsible for cell replication.

Animal used: Mice.

Drugs used: Free Doxorubicin, Magnetic Nanoparticles, DOX Loaded Magnetic Nanoparticles. The above mentioned therapeutic agents and animals used are taken from the

reference(Hu, 2024)For Justification of current study.

The procedure and evaluation tests, materials and instrumentations used to perform this study is based upon the protocols of the reference mentioned. (Hu, 2024; Shi,2021)

Result: The result in this study indicates the application of magnetic field can be useful to delocalize the Nanorobots and increase the rate of delocalization of nanorobots also indicates that the application of magnetic field on cancer cell leads to selectivity in targeting drug release and minimize the concentration to healthy cells by this we can decrease the toxicity on healthy cells.

II.Magnetic Nanorobots Paclitaxel loaded:

Principle: Paclitaxel is a potent Chemotherapeutic drug which directly binds and stabilizes the microtubules in cell which are responsible for cell division and stops the growth of tumor cells.

Animal Used: Rats

Drugs used: Native Paclitaxel, Free Paclitaxel, Paclitaxel Loaded Nanorobots(Pac-MNPs).

The above mentioned therapeutic agents and animals used are taken from the reference (Akhtar, 2020; 2022) For Justification of current study.

The procedure and evaluation tests, materials and instrumentations used to perform this study is based upon the protocols of the reference mentioned (Hu,2024).

Result: The result in this study indicated that the efficacy of Pac-MNPs to penetrate through BBB-Blood Brain Barrier. And also indicates that the effective locomotion of Pac-MNPs in systemic circulation.

III. Methotrexate-Loaded Superparamagnetic Iron Oxide Nanoparticles:

Principle: Methotrexate is used as the antiinflammatory, antiproliferative and immunosuppressive it inhibits the enzyme dihydrofolate reductase(DHFR) which is responsible for proliferation of cell components , DNA and RNA.

Test model used: Human cell Lines.

Drugs used: Free Methotrexate(MTX), MTX-SPION(Methotrexate Loaded Superparamagnetic Iron Oxide Nanoparticles).

The above mentioned therapeutic agents and animals used are taken from the reference[64]For Justification of current study.

The procedure and evaluation tests, materials and instrumentations used to perform this study is based upon the protocols of the reference mentioned (Shi, 2021).

Result: This study indicated that the Methotrexate Loaded Superparamagnetic Iron Oxide Nanoparticles showed sustained drug released and decreased toxicity to healthy tissues when compared to Free Methotrexate. And it also indicated that Superparamagnetic Iron Oxide Nanoparticles (SPIONs) can enhance the cancer cell targeting.

Table 3- Different types of nanorobots with their challenges, benefits and mechanism of action-

Type of nanorobot	Encapsulation material	Formulation	Mechanism Of action	Benefits	Challenges	
Magnetically guided nanorobots	Magnetic nanoparticles (Fe-iron oxide)	Doxorubicin-loaded magnetic nanoparticles	Uses external magnetic fields to guide nanorobots to the tumor site.	Precise targeting, non-invasive control.	Requires external magnetic setup, limited depth of penetration.	(Zang,2023; Chen, 2024; Ye,2023)
pH-sensitive Nanorobots	pH-sensitive polymers (e.g., poly(lactic-co-glycolic acid) (PLGA))	Doxorubicin in pH-sensitive nanocarriers	Releases doxorubicin in acidic environment	Targeted drug release, reduced systemic toxicity.	Potential variability in tumor pH, formulation complexity.	(Zhou,2024; Xu,2024; Jangharon, 2024)
Thermosensitive nanorobots	Thermosensitive liposomes or polymers (e.g., N-isopropylacrylamide)	Doxorubicin-loaded thermosensitive carriers	Releases drug when exposed to specific temperatures.	Controlled release, localized effect.	Requires controlled temperature application, risk of overheating healthy tissues.	(Aladeniyi, 2023; Xu,2024; Li,2023)
Ultrasound-responsive Nanorobots	Ultrasound-sensitive liposomes or gas-filled nanobubbles	Doxorubicin encapsulated in ultrasound-responsive nanoparticles	Drug release triggered by ultrasound waves.	Non-invasive, targeted release, real-time monitoring.	Requires access to ultrasound equipment, depth limitations.	(Teixeira, 2023)
Light-activated Nanorobots	Light-sensitive polymers or gold nanoparticles	Doxorubicin within light-sensitive nanocarriers	Activated by specific wavelengths of light, releasing the drug at the tumor site.	High precision, reduced off-target effects.	Limited to surface accessible areas, potential phototoxicity.	(Jayapriya, 2023; Xu 2022)
Enzyme-responsive Nanorobots	Enzyme-sensitive polymers (e.g., peptide-based carriers)	Doxorubicin conjugated with enzyme-cleavable linkers	Drug release triggered by specific enzymes present in the tumor microenvironment	High specificity, minimal systemic side effects.	Requires precise enzyme targeting, complex design.	(Saurabh 2023; Dattora, 2024);

Table 4-Additional nanorobots types formulation, material used, and mechanism of action

Type of nanorobot	Encapsulation material	Formulation	Mechanism Of action	Benefits	Challenges	
DNA-based Nanorobots	DNA origami structures	Doxorubicin encapsulated in DNA origami structures	Drug release triggered by specific molecular cues or environmental changes.	Customizable, precise control over drug release	Complex synthesis, potential immunogenicity.	(Wang 2024; Liu 2024)
Microbial Nanorobots	Genetically engineered bacteria or viruses	Doxorubicin-loaded bacterial or viral nanorobots	Utilizes microbes to deliver and release doxorubicin at tumor sites.	Self-propelling, active targeting.	Safety concerns, regulatory challenges.	(Sun,2023)
Biodegradable Polymer Nanorobots	Biodegradable polymers (e.g., PLGA, chitosan)	Doxorubicin encapsulated in biodegradable polymers	Gradual degradation of the polymer releases the drug at the tumor site.	Controlled release, reduced long-term toxicity.	Potential for incomplete degradation + formulation challenges.	(L.v,2024)
Hybrid Nanorobots	Combination of materials (e.g., magnetic + pH-sensitive polymers/Complex design, higher production cost.	Combination of different nanomaterials for doxorubicin delivery	Combines multiple mechanisms (e.g., magnetic and pH-sensitive) for enhanced targeting.	Multifunctional, improved targeting efficiency.	Complex design, higher production cost.	(Zhi,2024)
Chemical Gradient-guided Nanorobots	Chemotactic material (e.g., functionalized nanoparticles)	Doxorubicin-loaded nanocarriers guided by chemical gradients	Follows chemotactic signals to reach and release the drug at the tumor site.	Autonomous targeting, minimal external intervention.	Complexity in controlling chemical gradients, requires fine-tuning.	(Nie,2024)

Material selection for manufacturing/Fabrication:

The Ideal Characteristics of the fabrication material should be consists of (Wicki,2015):

- Biocompatibility.
- Motility and performance.
- Efficiency of loading cargos.
- Non- reactable with cargos.
- No deformation-high payload loading capacity.
- It should not stimulate immune responses when propelling in the body.

The composition of the MNR systems should contain (Elbialy ,2015) organic components such as polymers, Inorganic components such as metals and salts,if they are bacteria they

composed of biohybrid components in them. The polymers helps in the loading, transporting and releasing the payload at the targeted site. The polymers are also shows good stimulus effects like light, temperature, magnetic rays, ultrasound rays, enzyme reflexes, pH reflexes for better controlling of these systems whereas inorganic materials like metals and salts are responsible for preventing insoluble complex formation and enhancement in biodegradability.

Excretion and non-toxic conversion:

Generally, robots resemble structures made of metals or nondegradable polymers. Recently fabricated MNR devices have been made with metals that produce insoluble complexes and stimulate immune responses owing to the insoluble residues left in the body, leading to chronic side effects apart from cancer relapse (Elbialy 2015; Dilnawaz ,2012). Therefore, MNRs should be made up of biodegradable material if not the MNRs are retrieved immediately from the body or excreted from the body after the completion of the therapeutics. Without faults, microrobots are degraded by physiological functions that occur in the human body or they should be degraded by incorporating self-destructive components, thereby preventing hazardous adverse effects. Therefore, the fabrication material should be considered important so far (Zhou,2021).

Imaging and tracking Practicability of Micro/Nanorobots:

The monitoring and motion of MNRs are (Elbialy, 2015; Dilnawaz ,2012)essential when they are introduced into biological systems such as the human body; hence, real-time imaging and tracking in vivo is considered to be the most important factor. (Dilnawaz ,2012; Bhattacharya, 2023).Some types of imaging techniques, such as fluorescent imaging (FI), magnetic resonance imaging(MRI), ultrasound imaging(USI), and computed tomography(CT), have been used to track MNR systems. However, the use of significant words in tracking these devices requires improvement for precise tracking of better therapeutics. The precise tracking of these MNR systems is a challenging task because of the complex heterogeneous structures and dynamic environments present in the human body. It is important to note that the design of MNR systems should be compatible with imaging systems that are applicable, compatible with the disease, and compatible with the condition of the patient.

Physical parameters such as the shape, size, material used for manufacturing, and motility of the robot should be evaluated during the imaging process (Bhattacharya, 2023).

Finally, we can say that the MNR systems have the unavailability of particular imaging systems and are still delayed in pre-clinical approaches. Thus, work should be done to improve imaging systems that have ideal characteristics, such as enhancements in the resolution of imaging, motility detection, and most importantly, distinguishing between the MNR systems and the environments in the human body (Elbialy, 2015).

AI and Machine learning in Medicinal nanorobots:

From the time after the pandemic, computer CPUs have advanced as they can think and make decisions on their own because of their advancement in processing speed, and this self-decision making and thinking is designated (Das,2024; Zhu,2024) as Artificial Intelligence. Artificial Intelligence is the Intelligence where the computer can process the data, store the data, detect the data according to previous data, build models like our Imaginary Brain, show them visually, and provide accurate and precise structures and values. Artificial Intelligence can also be a good partner for humans, which helps in solving problems, reasoning, justification, translation, navigation, and guidance. However, despite all the amazement done by AI, artificial intelligence can work properly if there is data input to it, meaning artificial intelligence; the name itself indicates artificial means Provided not Natural. Natural intelligence means that humans who developed this mechanical partner to assist humans for their needs, but AI depresses Human Intelligence, and some technical experts expect that this gona be a dangerous mechanical human if it loses its control for misuse. That is, other thing.

(Ceylan,2018). Currently, artificial intelligence is used in medical fields such as prescription,diagnosis,education,nursing assistance, surgeries, and drug development; artificial intelligence is also a good assist and partner to doctors, as well as to pharmacists to minimize medical errors; in addition to diseases, patients suffer from medical errors; sometimes, it may cause death, which can be overcome by artificial intelligence, AI also now or in the future used by the Medicinal Micro/Nano robots, which

are revolutionary devices used in cancer treatment,diagnosis, and targeted drug delivery systems. Technicians, scientists, and various hardware companies are in the process of fabricating nanoscale CPUs and Nanoscale drug carriers that can be delocalized by their own thinking and with automated navigation systems in such a complex and dynamic environment in the human body. Figure-6.

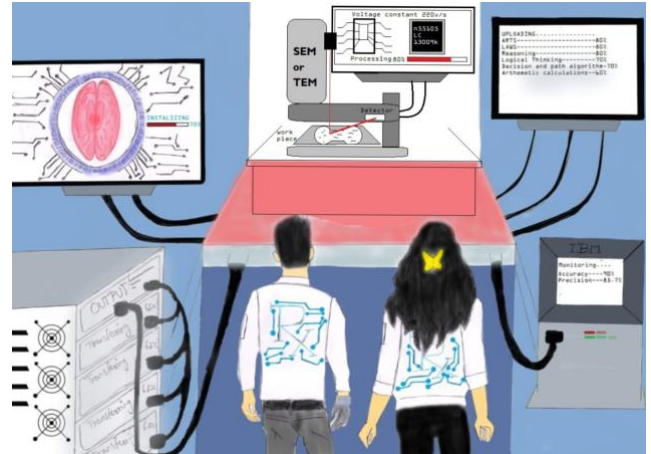


Figure 6-AI controlling, guiding nanorobots along with providing the necessary output, used for both treatment and diagnosis.

Machine Learning In Medicinal Micro Carriers:

Machine Learning is the subfield in the artificial intelligence where it is helpful in teaching computers to learn from provided data.(Medina-Sánchez,2017;Zhu,2024).The processing chip in Artificial Intelligence functions as its brain, containing millions of tiny transistors that mimic human brain neurons. These transistors are organized in layers to execute algorithms, receive input signals, and transmit output signals, facilitating communication between technicians and Nanobots, as well as among Nanobots themselves. These vast networks of transistors, known as neural networks, are capable of complex tasks such as learning intricate patterns, storing information, recognizing images (Ceylan,2018) and making decisions.

Neuro-Dynamic Programming:

Reinforcement Learning, also known as neuro dynamic programming, is a machine learning approach that instructs systems in decision-making, processing, and path recognition through environmental interactions. Examples include training a robotic dog for (Ceylan,2018;

Fernández-Medina,2020) deliveries by exposing it to external environments, and educating a logistics robot through interactions within its specific setting. This learning technique is primarily employed to instruct autonomous systems. Additionally, it is utilized to program nanoCPUs in microdrug carriers, enabling them to make independent decisions, navigate, delocalize, transmit diagnostic data as output signals, communicate with technicians and other microcarriers, and adapt to the complex and dynamic environments (Wang,2022) within the human body to achieve desired outcomes. Figure-7.

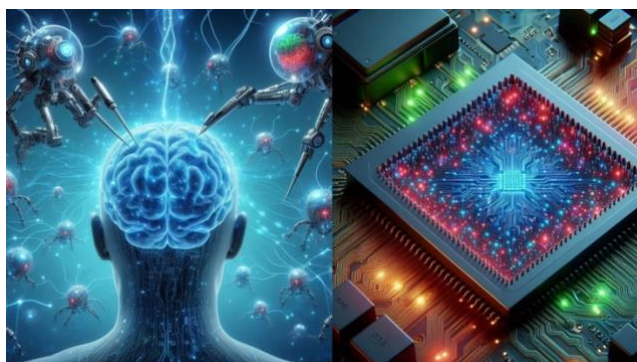


Figure 7-Neuro-dynamic programming; millions of transistors linked to AI brain(system).

Into the future of nanorobots in cancer treatment –

Artificial intelligence cannot be able to think like human intelligence because of their arithmetic thinking we all know that how (Zhu,2024) machines think .so in future we can expect better nano carrier imaging and tracking systems (Jakupovic,2018) which are improved with accuracy. we can raise the doubt about the present imaging systems but these only contain precise imaging.

According to present beyond imagination development in computer systems and medical field we can expect in future that is nano-robots or nano-carriers are upgraded with self energy source and Adaptive energy source,with individual processing chipsets and with efficiency in carrying of payload and self communication between nano-robots (Mukherjee,2024).

The current issues -

- Biocompatibility - Avoid the triggering of immune response or toxicity.
- Power Supply - Sustainable Source development
- Lack of using combination therapy.
- Need for biodegradable nanorobots.
- Cost-effective manufacturing.
- Need to address tumour heterogeneity.
- Need to over come BBB for brain cancers..
- Improvement in real-time monitoring (Wu,2023; Kim ,2024; Liu,2024).

To overcome these the future development may target on-

- 1)Enhanced targeting precision.
- 2)Combination therapies
- 3)Real-time monitoring
- 4)Adaptive drug delivery
- 5) Biodegradable materials (Wu,2023; van der Zanden,2020; Khan,2024).

1)Enhanced targeting precision- This field is evolving rapidly so as to improve therapeutic outcomes. Nanoparticles based targeting help in active targeting by using binding to overexpressed cancer receptor using specific ligands. Where as silk peptide nanoparticles improve efficiency of drug delivery by co-loading multiple therapeutic agents. Multiple therapeutic agents like photo thermal therapy and gene therapy enhances penetration of drugs along with tumours retention (Sandbhor,2024 ;Joseph, 2022). Figure-8.

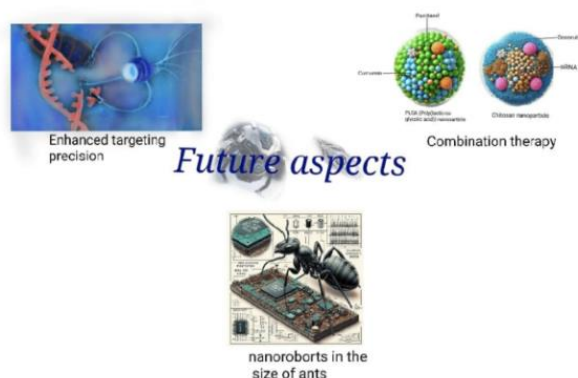


Figure 8-Future aspects.

2)Combination targeting precision-This allows multiple therapeutic agents to work together enhancing efficiency and decreased Side effects. Dual-drug loaded polymeric particles new designs conform that drug capsule optimization, bioavailability improvement and toxicity reduction can be achieved through computational methods. Chemoimmunotherapy causes a synergistic effect leading to improved patient outcomes as it can overcome the limitation of Single agent therapies. Metal-organic frameworks (MOFs) work as a multifunctional drug delivery system showing that they Can reduce drug resistance. These have limitations such as Scalability, vegulatory hurdles & potential toxicity which should be overcome (Ahmad,2022; Soni,2023; Zang,2024;He,2024). Figure-8.

003)Real time monitoring-The incorporation of these components is therefore expected to lead to significant gains in chemotherapy efficacy.During the process of treatment of cancer, self-guiding nanomaterials can indicate their position and the state in which they are found and hence give room for control of therapy(Su, 2023;Jin,2024).Such self-guiding nanomaterials can also be able to reach the target tumors by themselves, hence reducing negative side effects without the limitation of the high selectivity of the treatments(Su, 2023;Jin,2024). In vivo flow cytometry allows visualization of circulating tumor cells, which enabled scientists to explain how gold nanowires influence cancer spread (Pang ,2021; Su,2023). Fluorescein shadowing nanoparticle clusters makes it possible to visualize tumor enzyme activities as a function of the tumor's growth since fluorescence is proportional to the tumor growth(Pham-Nguyen ,2022;Ma;2023). Drug Release Monitoring is a stimulation-responsive metal-organic framework system is prepared, which can monitor the dynamic change of drug during the release process. Hence, it can help provide better focused therapy since less dosage would be needed(Liu, 2022;Su,2023).

4)Adaptive drug delivery -Besides, the improvement of these drug delivery systems, in which nanobots are employed for the treatment of malignant diseases, holds promise. In these systems, the properties of nanomaterials are used effectively in the targeting process by overcoming

the issues such as tumor heterogeneity and other physiological challenges to maximize specificity and effectiveness. Stimuli Development Systems Nanoparticles can be designed to be actively sensitive to the changes in external stimuli like pH and ultrasound waves, in order to drug exactly where dreadfully needed hence improving treatment effectiveness (Gu,2024; Pham-Nguyen,2022). This flexibility helps to ward off the challenges posed by the dynamic nature of the tumor's environment and therefore enhances the treatment (Zhang ,2024; Pham-Nguyen,2022). Vascular resting enhancement The use of the nanodrug delivery systems improves the pharmacokinetics of the anticancer agents, enhancing their bioavailability while minimizing their systemic toxicity. As a result of the targeted delivery of these properties, functionalized carriers are able to prolong the half-life of antimicrobial agents, which is highly relevant concerning the therapy of cancer (Singh, 2023; Liu,2022). Conclusion The invention of bio-inspired adaptable micro-medications has ushered in hope to transcend hurdles for instance the blood-brain barrier in increasing drug delivery, especially to such cancers as glioma, which have proved difficult in the past (Wang, 2024; Gu,2024). Further studies are required owing to the lack of balance between efficacy and safety in the practical use of these systems in various forms of cancer (Xu, 2024; Zang,2024).

5)Biodegradable materials-The gap has been hugely bridged by the development in nanobots-based adaptive drug delivery systems for cancer therapy in recent years. These systems exploit the exclusive properties of nanomaterials toward improving targeting capabilities and therapeutic delivery to the tumor location and addressing issues such as the intricately irregular interior structure of a tumor mass and biological barriers.These nanoparticles can be designed in such a manner that drug release is event-driven, which means it takes place in response to specific stimuli like pH or ultrasound at the desired location(Gu, 2024 ; Singh,2023).This is a form of elasticity that can serve to address one crucial challenge that occurs during cancer treatment known as the tumor microenvironment and how it alters during treatment(Zhang , 2024;Wang,2024).The therapy using the nanodrug delivery systems may not only take advantage of the vermiform anti-cancer agents but also the pharmacokinetic enhancement of their drug delivery systems. Functionalized

nanocarriers can extend the extended periods of defense of the drugs while guiding them into specific compartments in the body, which is significant in the treatment of the cancer (Singh, 2023; Shi, 2024). The hope that can be shown by the development of adaptable microdrug with bioinspired tendencies can help in finding solutions for such challenges as blood-brain barriers and weight delivery in drugs for difficult tumours like the glioma. For example, (Wang, 2024; Ding, 2023). It remains that there should be further studies on these application areas of cancer to make them better, in certain areas where improvements are needed, for effective use at clinics (Xu, 2024; Fang, 2024).

Conclusion –Nanobots are the most favoured type of targeted drug delivery system. Where these are used in various fields their role in cancer treatment is important. There are multiple types of nanobots available each having its advantages and disadvantages even so we are not currently in the stage to use them for daily therapy and we can see these only in special cases so there is a need for making more accessible nanobots which are cost-effective same goes for the drug doxorubicin, identification of more such drugs is needed for combination therapy. Finally, there is great hope for nanobots in the future where significant changes will occur mainly through AI.

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