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NANOROBOTS IN MEDICAL APPLICATIONS

Sharayu Govardhane*[1] and Mansi Waghchaure[1]

[1*]C.U. Shah College of Pharmacy, S.N.D.T Women's University, Maharashtra, Mumbai, India.

ABSTRACT

The purpose of this paper is to draw attention towards the emerging fields of nanotechnology. Nanomedicine is a therapeutic process which will turn out to be a phenomenal drug delivery system. Nanorobots is an advanced technology and currently, the research is in progress to use nanorobots in diagnosis, treating and preventing the disease. This is for improving the human health. The main purpose of nanorobots is to cure many dreadful diseases in human body. Nanorobotics includes the study of design and construction of robots. The technology works at an atomic, molecular or cellular level. Nanorobots are the tiny structures ranging about 1-100nm. The content of this paper will focus on the recent advances in nanorobotics and how the technology will be utilized in the medical application.

KEYWORDS

Nanorobots and Nanomedicine.

Author for Correspondence:

Sharayu Govardhane,

C.U. Shah College of Pharmacy,

S.N.D.T Women's University,

Maharashtra, Mumbai, India.

Email: sharayugovardhane@gmail.com

INTRODUCTION

Nanotechnology is positively impacting a part of nearly every industry including healthcare. The application of nanotechnology to healthcare – also called nanomedicine[1]. Nanotechnology allows working at molecular and atomic level[2]. A nanometer is a billionth of a meter or ten times the diameter of hydrogen. One of the emerging trends in nanotechnology is NANOROBOTS[3]. Basically, nanorobot is a very small robot used to perform some precise tasks in the body. In 1986, K. Eric Drexler first introduced the idea of using nanorobots for treatment in a human body and this idea was further studied and designed by Robert A. Freitas. The other words like Nanobots, nanoids,

nanites, nanomachine or nanomites also represent nanorobots. Respirocytes, clottocytes and microbivores are some of the types of nanorobots which were designed by Robert A. Freitas[2].

Medical nanorobots[4,5] offer diagnosis and treatment in the disease like diabetes. These are capable of detecting and destroying cancer cells as well. The nanorobots like chromallocytes can be used in critical therapy like Chromosomal Replacement Therapy (CRT) which works at the cellular level. Using this technology one can directly target a particular cell instead of targeting tissues or organ.

WHAT ARE NANOROBOTS?

Nanorobots are the nanotechnologically derived nanomachines which work at nano level in the body. The word nanorobot consist of NANO and BOT. Nano means extremely small and bots mean robots. Nanorobots are the electromechanical devices measured on the scale of nanometers. Nanotechnology helps to design, program, manufacture and control robots at the nanoscale which have a diameter of about 0.5 to 3 microns and will be constructed within dimensions in the range of 1 to 100nm[6]. Nanorobotics is the study of nanorobots. Nanorobots are capable of manipulating objects that have dimensions in the nanoscale range with nanometer resolution. Nanorobots can repair the cell damage by using surgical therapeutic procedures in the human body and hence it is an advanced tool for the treatment of various human diseases and biological system. During surgery, doctors can communicate with a robot using acoustic signals which needs to be encoded using decoding system. The wave frequency of signal ranges between 1-100 MHz.

COMPONENTS OF NANOROBOTS

Various components in nanorobots includes

Nanobearings and nanogears

Bearings and gears are manufactured by either ball and stick or space filling representation or both. The bearing is made up of 206 carbon atoms, silicon, oxygen and hydrogen. It contains a small shaft which has 2.2nm diameter rotate in ring. The combination of ring and shaft gives low resistance in shaft rotation.

Molecular gear assembly is 4.4nm long, 4.3 nm in diameter and has molecular weight 51009.84 Da and has 12 moving parts. The gear is made up of silicon shell with sulphur atom termination[13].

Payload

It is a void section which holds the drug. Nanorobot when inside the body releases the drug through payload on the site of action.

Micro-camera

It helps the controller to navigate the path of nanorobot in the circulatory system. It helps in monitoring the working of nanorobots[7,8].

Electrodes

Electrodes could have the ability to make battery with ions present in the biological fluid. These control may be protruding which can be used to kill tumour by producing electric current and inflaming the surface control can be obtain which can be used to kill tumour.

Laser

Laser embedded nanorobots are used in the case of destruction of plaques in arteries and blood clots[8].

Ultra-sonic signal generator

Ultrasonic sounds are often utilized with the help of nanorobots which would irradicate kidney stones.

Swimming tail

Function to provide mean of propulsion to travel inside the body against the flow of blood.

Nanocomputers

For the efficient activity nanorobots essencially requires onboard computers. This is a helpful tool to control nanorobot for the physicians[13].

For activity, nanorobots are embedded with the swarm intelligence. Swarm intelligence is a technique embedded for the artificial intelligence. The three types of swarm intelligence are ant colony optimization (ACO), artificial bee colony (ABC) and swarm optimization (PSO).

For motility, the nanorobotots are provided with motors and manipulator arms or mechanical tail. The nanorobots can recognise certain stimulus like chemical stimulus which would help them for the detection of target site.

APPROACHES FOR ASSEMBLY OF NANOROBOTS

1. Self-assembly and directed parts assembly- In this, the assembly is according to the natural behaviour of parts. Parts automatically joins because of their affinity towards another parts.
2. Positional assembly- in such system, manufacture has to assemble parts manually. The investigator may use mechanical robotic arm or microscopic set to pick up parts and assemble them[18].

DESIGN OF NANOROBOT[9,10]

The software NCD (nanorobot control design) is a system for a fast development platform for medical nanorobots investigation and 3D prototyping. The NCD simulations show how to interact and control a nanorobot inside the body. The advanced nano mechatronics simulator provides physical and numerical information for nanorobot task-based modelling. The design of nanorobot is comprised of integrated nanoelectronics and components such as molecular sorting rotors and a robot arm (telescoping manipulator) derived from biological models.

To avoid the problem associated with the incompatibility in the body, the external membrane is manufactured of diamondoid substance. In order to overcome immune reactions and to decrease fibrinogen adsorption a structure called artificial glycocalyx is adhered. The action of these chemotactic sensors is to identify the molecules. The affinity for a particular binding site varies from sensor to sensor. The design of sensor and tolerance is affected by many factors like environment and function to be accomplished. As these sensors can identify the hardels, perhaps the nanosensors are used which enables to identify the hardel within 1mm of range[11].

DESIGN ATTRIBUTES OF NANOROBOTS[12]

Size and shape- the shape of nanorobots mainly based upon its activity and purpose. Mainly the smaller size robots are utilized. The structure enables easy movement in biological fluid. Tail structurally similar with flagella is utilized for easy movement.

Sensors- For proper functioning nanorobots must be capable of sensing borehole and reservoir type.

- Reservoir fluid type
- Reservoir temperature
- Formation pressure
- Fluid analysis

Means of mobility or propulsion- Self-propulsion mechanism.

Power generation- The power needed for proper functioning is small, probably 10-100 picowatts. The power required can be generated from:

- Power from fluid flow
- Power from reservoir temperature
- Power from friction with rock fabrics
- Downhole fuel cell generation from in-situation hydrocarbon.
- Use of downhole recharge station.

Data storage- Quantum computing helps in storing nano-sized data storage.

Telementry and transmission-

Control and navigation- It provides the ability to control nanobots from the surface.

NANOROBOTS: THE FUTURE OF MEDICINES

Minimally invasive treatment approach is the major requirement of todays world. For this, scientists are working on such treatment approaches which would not cause any pain and discomfort in patients. Researchers are trying to develop such effective methods of diagnosis and identifying change in body without any invasions and observe patient for longer duration. The ongoing research mainly focus on developing nano-scale robots from nano compounds.

ADVANTAGES OF NANOROBOTS OVER CURRENT MEDICAL TECHNIQUE

The main advantage of using nanorobots is the safety and reliability of the procedure. Nanorobots will overcome the following problems associated with conventional methods-

1. Incisions on body takes long time to heal
2. Anaesthesia – allows the long term unconsciousness in patient. Not suitable for short term therapy.
3. Success rate of critical surgeries is less.
4. A simple mistake in critical surgery leads to serious effects or may be death of patient.

The advanteges of using nanorobotic method is

1. No tissue injury or trauma
2. Less recovery time
3. Post operational care is less
4. Continuous troughout body monitoring
5. Quick respose to the therapy
6. Saving monitored data and recognise the pattern.
7. Pattern helps to identify the onset of ailment.
8. Delivery of drug from payload

CHALLENGES

The major challenge in manufacturing of this is the size of nano-device and the physics at the nano scale. As the size is reduced, the surrounding environment and forces will affect the activity of nanorobot. These nanorobots behaves like pseudo molecules as they are as small as molecules. The surrounding like fluid effect, viscosity and some electrostatic forces would affect the activity. The motion of nanorobots may get affected by the thermally triggered collision in Brownian motion. The forces acting on nanorobots may lead to the deformation of device. This changes the characteristics of a nanorobot.

Also inserting the artificial intelligence in such a small system is a difficult task. For this the nanodevice should be enough rigid. The self-assembly of the parts overcome this problem and make the system rigid.

The another challenge associated with manufacturing of nanorobots is power generation and power storage.

NEMS and MEMS is another technology used which is biocompatible. Nanorobot can be prepared using this technology.

PREDICTED USE OF NANOROBOTS

The use of nanorobot has revolutionary impact on the field of medicine. Nanorobots can be used to deliver controlled release medicine and delivers to the exact location. The nanorobots are able to overcome the immune system attack

CATEGORIES OF NANOROBOT

Robert A. Freitas Jr had developed different forms of nanorobots are[2].

1. Respirocytes
2. Clottocytes
3. Microbivores

RESPIROCYTES

Red blood cells have a protein called haemoglobin which carries oxygen molecules throughout the body. RBC's remove carbon dioxide from a body and transports it to lungs. Respirocytes are the artificial red blood cells. These are 1µm in diameter. The respirocyte is made up of 18 billion atoms which are arranged in diamondoid pressure tank. This tank can take up to 3 billion oxygen and carbon dioxide molecules[13]. The shell of diamondoid material has 1000 atm pressure with a reversible molecule-selective pump. Respirocytes carry O_2 and CO_2 throughout the body.

Respirocytes can deliver up to 236 times more oxygen molecules to tissue than natural blood cells.

STRUCTURE OF RESPIROCYTE

There are 3 types of rotors. Among the three, one carries and another delivers oxygen molecules in the body. The 2nd nanorotor of rotor take up carbon dioxide molecules from blood circulation and transport it into lungs. The 3rd rotor takes up glucose molecule as a source of energy. There are 12 identical pumps which release gas molecules[14].

When respirocytes pass through lung capillaries they take up oxygen molecules and releases carbon dioxide molecules. The release of carbon dioxide molecules depends upon the partial pressure of O_2 and CO_2. In lung capillaries the partial pressure of oxygen will be eminent while the partial pressure of carbon dioxide would be less. Hence the onboard

nanocomputer governs the sensors to pack the O_2 molecules. The water ballast chamber maintains the buoyancy.

After the function is done, these respirocytes are removed from blood by respirocyte activating protocol. This protocol is known as Nanapheresis. The blood from a patient is passed through centrifugation apparatus where the ultra-sonic commands are given. Nanorobots maintains the neutral buoyancy while solid blood components won't. The solid blood components are added back into the circulation.

CLOTTOCYTES

The theoretically designed nanorobots i.e clottocytes are artificial platelets which perform the function of natural platelets. Hemostasis is the naturally occurring blood clotting mechanism. Enjury to the endothelial cells expose the collagen to platelets. This leads to platelets activation and starts the blood clotting mechanism. This whole process takes around 2-5mins. In some patients, this clotting mechanism occurs irregularly. This abnormality is generally treated using drugs such as corticosteroids. But these drugs leads to many side effects such as hormonal secretion imbalance, allergic reactions etc[15].

Clottocytes can perform this process in approximately 1sec. the response time os these nanorobots is 100-1000 times faster than the natural hemostasis system. This nanorobot is usually 2µm in diameter and is powered by serum-oxyglucose, and contains fibre mesh which is surrounded by the soluble film coat.

The fibre mesh would be bio-degradable. When the fibre mesh comes in contact with plasma it is converted into the sticky mesh by dissolving the soluble coatings. The formation of sticky mesh would be blood group specific.

As the clottocyte enters the damaged blood vessel, the sensors actively detect the variations in the partial pressure. This change in partial pressure may indicate the blend out of the body. The reliable communication system is required to control the system. In the process, the acoustic pulses are transmitted from one to another. This allows rapid propagation of signal cascade. The one mesh will overlap neighbouring mesh, overlapping it and engage RBC's in the process of blood clotting.

The major risk associated with this is the additional activity of mechanical platelets which triggers the intravascular coagulation ressponding in micro-thrombi.

MICROBIVORES

Microbivores are artificial white blood cells. These are also known as nanorobotic phagocytes. They trap, absorb and digest pathogens by the process of phagocytosis. Hence these are also known as nanorobotic phagocytes. These nanorobots are utilized for clearance of respiratory, cerebrospinal bacterial infections.

Microbivores are made up of sapphire and diamond. The basic components of microbivores are

1. A reversible binding site.
2. A telescoping grapples
3. A morcellate chamber.
4. Digestion chamber.

In functioning of nanorobots, the bacteria which is to be targeted adheres to a receptor binding site on the surface of microbivores. The telescopic grapples comes up from the surface when bacteria bind to the surface and anchors security. The grapples are used to take bacteria from binding site and insert into the ingestion port. The bacteria is minced into nanoscale pieces. The digestive enzymes are encorporated into the digestion chamber during its manufacturing. The morcellate is reduced to amino acids, free sugars, mononucleotides and free fatty acids. These nanorobots consist of an exhaust port. The small molecules are discharged through this port. The nanorobots exit the body through the kidneys and urine.

The entire cycle takes around 30secs. To avoid the chances of sepsis or shock, bacteria is converted into non-antigenic molecule. Microbivores act 100 times faster than antibiotics and posses no the of multiple resistance[2].

MEDICAL APPLICATIONS OF NANOROBOT

Medical nanorobots can be used to perform various functions in diagnosis, monitoring and treatment of diseases. The nanorobots have ability to deliver drugs to target sites or areas in the human body. The use of nanorobots advances biomedical intervention with minimum invasive surgeries. It also helps patients who need constant body functions monitoring, or ever improve treatments efficiency through early diagnosis of possible serious diseases. The advanced nanorobotics is to employ nanorobots to work at nano-level.

Cancer treatment

Presently available therapy for the treatment of cancer is radiation therapy and chemotherapy. The technology like nanorobots can be used to detect and cure cancer cells. Functions like searching for tumours, diagnosis and destruction by nanomanipulation can be performed and coordinated by nanorobots. The use of nanorobots in cancer therapy will reduce the side effects like nausea, vomiting, decreased immunity, alopecia[18].

Nanorobots can detect the tumour cells in the early stages of development and reduces the severity of the stage. Nanorobots provides non-depressed therapy for the patients.

Detection of cancer cells[16]

Nanorobots with chemical biosensors can be used for detection of tumour cells in early stages of development inside the patient's body. Hence a bioelectronics based hardware architecture is utilized for the function of nanobots in cancer treatment. The nanorobots are able to distinguish between different cell types that are the malignant and the normal cells. In the detection, nanorobots detect the surface antigens which are different for different cell types. For this purpose, it uses chemotactic sensors which are antigen-specific.

Another approach is the detection of different levels of E-cadherin and β-catenin in the primary and metastatic phases. E-cadherin is a calcium-regulated adhesion molecule which long-range in epithelial cells. It is a classic tumour suppressor gene which acts as a biomarker for the detection of cancer cells[19].

Nanorobot architecture

Difference in temperature, concentration of components in bloodstream defines the structure of nanorobots. Depending on the different gradients in temperature, the concentration of chemicals in the bloodstream, and on electromagnetic signature the design of nanorobots is based. CMOS VLSI (Very Large Scale Integration) Systems design using deep ultraviolet lithography provides high precision and an advanced way for manufacturing nanodevices and nanoelectronics systems. For validation of designs and to achieve a successful implementation, the VHDL (Verification Hardware Description Language) system has become the most common methodology utilized in the integrated circuit manufacturing industry[16].

Chemical sensors

Chemical nanosensors are embedded in the nanorobot to monitor E-cadherin gradients. Therefore, nanorobots programmed for such task can make a detailed screening of the patient whole body. In some nanorobot architecture, mobile phones are connected with bots to collect the information. In this, the electromagnetic waves are used as command and which gives the current status of a patients body.

Power supply

CMOS is used to keep the telemetry system secure and save energy to keep the nanorobot in operation[20].

Data transmission

Chemical signalling is used for the communication in nanorobots. Single-chip RFID is embedded into nanorobots. (Radio Frequency Identification Device) CMOS based sensors.

Signal implementation

The NCD (Nanorobot Control Design) software is used for nanorobot sensing and actuation. The architecture also includes integrated nanoelectronics. The system also includes the use of a mobile phone integrated system. This will give early detection of E-cadherin levels and smart way for the chemotherapy treatment. This information

may help doctors on detecting malignant tissues in initial stages of development. The exterior shape consists of Diamondoid material to which the artificial glycocalyx surface is attached which reduces the fibrinogen and other blood proteins adsorption and bioactivity, which ensure sufficient biocompatibility to avoid immune system attack[17].

Nanorobots in the bloodstream

The nanorobots maintain their positions near the blood vessel walls to improve the detection response and biosensing capabilities. After the one nanorobot is attached to the target it is programmed to attract other nanorobots to help ahead for the incisive chemotherapy on the tumour target. It will also give the accurate position of a tumour to doctors using the software. Chemical concentrations and signal intensities can attract or repel the nanorobots at the target and it estimates the number of bots present at the site. Hence, nanorobots stop attracting others as enough number is present. The number may be present on the stage of cancer or tumour size.

Following control, methods are implemented in the working of nanorobots

1. Random: nanorobots reaches the target cell using a Brownian motion.
2. Follow gradient: nanorobot monitors E-cadherin level and follows the gradient to reach the target. If it does not get sufficient intensity signal, nanorobots continue to flow without any action in the blood stream.
3. Follow gradient with attractants: this is same as above control system with improved ability to find the target by using integrated nanosensors.

Practical approach of nanorobots in cancer detection and treatment- PHARMACYTE[18].

Pharmacyte is a self-powered, capable of digitally precise transport, timing, and targeted-delivery of pharmaceutical agents to specific cellular and intracellular destinations within the human body using computer controlled medical nanorobot system. The size of pharmacyte is smaller than RBC and WBC hence easily pass through blood vessels and capillaries. The size of pharmacytes is 1-2µm and carries the drug load of $1\mu m^3$. Molecular markers and chemotactic sensors are encorporated into pharmacyte. The pharmacyte escapes the phagocytic process as they do not form obstruction in small blood vessels. Pharmacyte can be used as nanomedicines in the processes like an initiation of cell apoptosis in tumour cells and controlling the signal cascade in cells. Pharmacytes tag target cells with biochemical natural defensive or scavenging systems. This is called as phagocytic flagging[19]. The same mechanism is observed in T-lymphocytes. A lipid known as Phosphatidylserine is present inside the plasma membrane of a normal cell. But during apoptosis, it comes on the surface. Cells bearing this substance is identified and removed by the process of phagocytosis with the help of macrophages. This same mechanism is followed by pharmacytes. Pharmacytes on detection of cancer cells get attached to it and releases the drug from the payload[20].

For the movement of pharmacytes, they are provided with mechanical cilia and a mobility system. Pharmacytes can be collected after their use once they releases the drug from drug cavity. These nanorobots might be recharged, recycled and used in another patient for the same purpose.

Nanorobots in diabetes[21]

What is diabetes

For the appropriate working of human metabolism, the normal glucose level in the body is necessary. The level of glucose in the body is measured in the diagnosis of diabetes. For the normal working of gastrointestinal cholinergic nerve and skeletal muscle function activities, protein hSGLT3 is important. The protein is essential factor in the regulation of extracellular glucose. This protein also acts as marker for measuring glucose level.

Small blood sample must be taken by patients having diabetes to monitor and manage blood glucose level. This procedure is very inconvenient and uncomfortable. To avoid this kind of problem the level of sugar in the body can be observed via constant glucose monitoring medical nanorobots. This information can help doctors and specialists to provide a real-time health care, improving the

patient's medication regimen. It gives the glucose monitoring throughout the body. The nanorobots provides the body scanning of serum glucose level. Examination of information collected from various parts of body allows accurate level of the rate of change of glucose concentration in the blood which is passing through particular organ, tissue, capillary bed, and specific vessel. Nanorobots gives a specific level of the rate of change of glucose concentration in the blood. Nanorobots also dtects which tissues may have suffered diabetes-related damage, and to what level.

Characteristics of nanorobots

The size of nanorobot is approximately 2µm. Hence the nanorobots are free to move in blood circulation. The nanorobot design includes integrated nanoelectronics. Nanosensors can be useful for therapeutic treatments and medical instrumentation. The nanorobot is not attacked by the white blood cells as it is biocompatible with the system. The outer structure is made up of diamondoid material which is covered with the glycocalyx surface. Complementary Metal Oxide Semiconductor as nanobioelectronics protocol is used in the system. Chemosensors incorporated in the system is required for the modification of hSGLT3 protein glucosensing activity. The system can indicate if a person needs any injection (insulin) or any other medication. The image obtained from NCD shows inside view of blood capillaries, BBC's and nanobots.

Nanorobots flows with the RBCs through the bloodstream and detect the glucose levels. At a typical glucose concentration, the nanorobots try to keep the glucose levels ranging approximately 130mg/dl as a target for the Blood Glucose Levels (BGLs). A variation of 30mg/dl can be adopted as a displacement range. If the significant change in glucose level is detected by nanorobots, the collected information is transmitted to cell phones using RF signals. Nanorobot transmit the signal and gives alarm when the patients blood glucose level reaches the critical value. Nanobots enables a more effective diabetes treatment and helping patients to achieve a healthier and more comfortable lifestyle.

Nanorobots in heart surgery

Blood vessels of heart supply blood to the body. Due to the deposition of fatty materials, this flow gets restricted which leads to heart attacks and damage to vital organs. This also causes the narrowing of the coronary artery. To overcome these problems presently the heart by-pass surgery or angioplasty surgery is used.

Coronary Artery Bypass Grafting Surgery (CABS) is used to treat the coronary artery disease i.e the narrowing of the artery. Coronary artery supplies oxygen and nutrients to the heart muscles Autologous vein is used for grafting in CABG. Obesity, sternal wound infection, leg infections, and atrial dysrhythmias are some of the adverse effects associated with CABG surgery[22]. In the CABG surgery, incisions are made in the middle of the chest. The global mortality rate of 12.1 % and the average national rate of 6.2% is observed[23]. The surgery involves the open heart surgery in which the incision is made in the middle of the chest. For the grafting purpose, leg vein is used. The one end of the vein is attached to the coronary artery and another ebd to the aorta. This surgery takes about 4hrs time[24].

The conventional method possess some risk associated with patients health. To avoid this, nanorobots can be utilized to prevent these actions. Nanorobots are safe as well as fast and they provide better technique to destroy the plaque deposited in the vessels.

Properties and components of nanorobots used in heart surgery

The nanorobots employed for this function consists of an interior and exterior surface. The exterior surface directly comes in contact with the external environment and chemical substances in the body. But the interior surface does not as it is vacuum closed so that no liquid will enter into it. The nanorobot possesses the passive diamondoid surface which makes it biocompatible in the body. The diamondoid surface is smooth and flawless so as to prevent leukocytes activity. The outer surface is chemically inert and has low bioactivity.

For the propogation inside the body, an electric motor is utilized. Microprocessors controls the overall operation. The radioactive material is also incorporated on the outer surface so as to trace its location in the circulation. The magnetic switch is also provided. This magnetic switch provides the on-off function for the activity inside the body.

Introduction of nanorobots in bloodstream

The nanorobots are administered through larger diameter blood vessel. The artery should be such that it will be travel to get access to most areas in minimum time. The suitable choice for this is the femoral artery in the leg. The artery is the easy access point to the systemic circulation and helps in the operation that requires connection to bloodstreams.

Movement of nanorobots in the circulatory system

Active propellors embedded into the structure are used for movement inside the body. Electric motors with shrouded blade structure is utilized to avoid damage to the surrounding tissue during inevitable collisions.

Movement towards the site of plaque

To differentiate between the healthy and unwanted cells, long range and short range sensors are encorporated into a structure. The long range sensors give the site of plaque closely and hence these are used. Radioactive fluid is incorporated into the bloodstream which follows the same path as that of nanobot. This can be used to trace the exact location of nanorobots inside the circulatory system. The path is tracked by fluoroscope or any other radiosensitive imaging system is utilized. This information is used to generate the 3D map of track followed by nanorobot. At the target location, internal sensors are used to trace and monitor the plaque. TV camera gives a more precise location. The change in temperature is sensed by arterial thermometers associated with short-range sensors. The maximum temperature variation limit is set into nanorobot. When temperature more than the limiting range is sensed by sensors, the nanorobots start working. The particular area will be destroyed by the rotating needle attached to the nanobots.

Targeting the plaque

As the nanorobot senses the location of plaque activation of the rotating needle and diamond chipped burr will take place. This will grinds the plaque into microparticles. Cutting procedure is continuously monitored by a camera so as to observe that blade will not harm the neighbouring tissue. These microparticles then travel through the circulation without producing harm. Then these are excreted out of body.

Recovery from the body

After the nanorobot is done with its activity, it is supposed to be removed from the body. For this purpose, the nanorobot is guided to such blood vessel which is easily accessible from outside. These can be removed by performing small surgery.

In emergency conditions

In some emergency condition where surgeon has to stop the nanobot system, the magnetic switch is given. This magnetic switch serves as an on-off system. When the magnet is slid over the nanobot for 1st time, the system will be switched on i.e nanorobots activates. This movement of the magnet in one direction only switch on the system. If in the operation of removing plaque one has to stop the working of nanorobot, shutting down of the system is the only option by moving the magnet bar. This will terminates all the running functions of this nanomachine[25].

Nanorobots in brain aneurysm detection

A brain aneurysm is weakening of blood vessels in the brain which forms bulging in which blood gets filled. Aneurysms are not always life-threatening. But the bursting of an aneurysm can serve the complications. Bursting leads to spilling blood into the surrounding tissue and also associated with the stroke, permanent nerve damage, or death. Mostly the aneurysm rupture may cause a subarachnoid haemorrhage i.e bleeding into the space between the skull bone and the brain. Aneurysms are acquired and are more common in patient with certain genetic diseases. In most cases, a brain aneurysm does not cause symptoms and hence goes unnoticed. This condition is mainly diagnosed using Computed tomography (CT) scan, Computed tomography

angiogram (CTA) scan, Magnetic resonance angiography (MRA).

The treatment of an aneurysm depends on age, size of an aneurysm, any additional risk factors, and overall health of the patient. The risk associated with a small aneurysm rupturing is low and its surgery is risky, doctors usually don't suggest the operations. Doctors usually suggest the ways to keep blood vessels healthy as possible and managing high blood pressure and smoking. In case of a painful aneurysm or previously ruptured aneurysm causing pain, doctors may suggest surgery.

For this complex procedure, doctors can use nanorobots to overcome the complicated conditions. The nanorobots used in a brain aneurysm contains a nano-integrated circuit version that uses hybrid materials, photonics, and wireless communication for manufacturing and control. Three key required pieces to advance the development and implementation of medical nanorobotics are a) equipment prototype b) manufacturing technology c) inside body transduction. Equipment prototype and manufacturing technology are same as that of robots in cancer, diabetes and heart surgeries. The nanorobots detect the level of NOS i.e Nitric Oxide Synthase an overexpressed protein inside an intracranial blood vessel. The normal level of NOS is around 1µm. In nanorobot architecture, the antibody CAB002167 is used to modulate the sensors. The antibody attached serves to identify the locations of NOS which is recognised by a change in gradients of brain enzymes. Carbon nanotubes can be served as better material for the nanobiosensors. Once the nanorobots are inside the blood vessels start moving with the fluid. Nanorobots starts searching for vessel deformation and the location of a brain aneurysm. NOS signals are detected as the gradient changes which denotes proteomic overexpression. Nanobiosensors gets activated as the robot moves closer to an aneurysm, emitting the RF signals to the connected device. As the nanorobots keep flowing, the chemical signals become weaker, deactivating the nanorobot transmission. Red cells and nanorobots flow with the bloodstream until they leave the vessel.

If the nanorobots detects the signal of NOS at low quantities, it generates a weak signal lower than 50nA. in this case, nanorobot will ignores the signal considering it as normal. If the NOS concentration exceeds the expected level i.e higher than 90nA, nanorobots get activated and start emitting electromagnetic signals which are detected by a receiver. From this position of nanorobot as well as aneurysm is determined[26,27].

Nanorobots in dentistry

Considering the growing future interest in the field of dentistry, nanotechnology leads to the emergence of a new field known as nanodentistry. Nanodentistry includes local anaesthesia, dental renaturalization, cure of hypersensitivity, orthodontics, dentifrices etc.

Dental perspective for the nanorobot identified by researchers Goene *et al*, 2007[28], Freitas, 1999[19], which includes atomic elements required to prepare nanoparticles and the construction of nanoscale object.

These nanorobots might use specific mobility system to navigate, acquire energy, sense and penetrate the human tissue and ultimately causes manipulations in surrounding environment. On-board computers manage the function of nanorobots which are supported with pre-identified functional events and commands. The instructions are conveyed by means of acoustic signals.

Nanorobots in oral anaesthesia

A colloidal suspension encorporated with active micro-sized nanorobots are instilled into patients gingiva. These nanorobots reacts to the stimulus provided by dentist. Nanorobots reach pulp by migrating into gingiva sulcus, lamina propria or dentine tubule. As soon as nanorobot reaches pulp, they shut down all the senses by controlling nerve impulses. Faster action without any side effects and complication is the advantage of using this method. After completion of work, dentist orders the nanorobots to restore all sensation. Nanorobotic anaesthesia offers greater patient comfirt and compliance, reduce anxiety, sensitivity and

controllability of analgesic effect. It provides an avoidance of most of side effects and complications[29].

Nanorobots in hypersensitivity

The hypersensitivity is observed when there is change in pressure transmitted to pulp. The hypersensitive teeth have eight times higher surface density of dentine tubules. The diameter of dentine tubule becomes twice as large as the non-sensitive tooth. So the nanorobots used in such conditions particularly and specifically occlude tubules in minutes, giving patient a quick relief and cure[31].

Nanorobotic dentifrices

Nanorobotic dentifrices are delivered in the form of mouthwashes or toothpaste. These preparations can cover all subgingival surfaces thereby metabolizing trapped organic matter into harmless and odourless vapours. Dentifrices can identify and destroy pathogenic bacteria that exists in the plaque. These mechanical devices safely deactivated themselves when swallowed[30].

Cavity preparation and restoration

The cavity preparation is a very precise process. It is restricted to the demineralized enamel and dentine and hence provides maximum conservation of sound tooth structure.

Major tooth repair

Nanorobots are manufactured to replace the whole tooth with minerals and other components which helps in complete dentition replacement therapy[30].

Tooth durability and appearance

To enhance the tooth appearance and durability upper enamel layer are replaced by artificially bonded materials like Sapphire. Sapphire is susceptible to acid corrosion but still can be used as the cosmetic alternative[30].

Orthodontic treatment

The frictional force is required to slide the tooth along an archwire. This type of orthodontic force may causes loss of security and tooth resorption. In future, orthodontic nanrobots would act on periodontal tissues. This will allow rapid and painless tooth straightening, rotating and repositioning within small time[29].

Maintenance of oral hygiene

To maintain the oral hygiene, a mouthwash containing nanorobots can recognise and kill pathogenic bacteria. This will allow the flourishing of harmless flora of the mouth. This device will detects particles of food, plaque and are capable of lifting it from teeth to be thrown away. As this system is given in the form of the liquid, it is able to reach most of the surface area of the mouth cavity[29].

Nanorobots in gene therapy

Most of the human diseases are due to improper functioning at the cell level. The cell action and protein synthesis is regulated by gene expression. Hence, many diseases are characterised either due to faulty chromosome or gene expression. For such defects presently employed therapy is the incorporation of new genetic material into the cell by bacteriophage, virus, dendrimeric, nanoparticulate, cationic liposome, plasmid and phospholipid microbubble, stem cells, bacterial or any other vector to rupture the cell membrane. Due to immune responses to antigen of viral carriers permanent gene replacement has failed. Electroporation[32], nucleofection[33] and laser are some of the techniques employed for this therapy. Direct extraction of the chromosome has been practised since the 1970s[34]. The nuclear transfer and nuclear transplantation are the effective techniques used nowadays.

Replacing an existing set of chromosomes with the new set of chromosomes is known as Chromosome Replacement Therapy (CRT). Full replacement of original DNA may lead to some defects like XXY syndrome, congenital heart disease and may also lead to cancer[34,35]. The use of nanorobot for this is a hypothetical concept. The nanorobots used for cell repair is known as CHROMALLOCYTES[36]. These chromallocytes are infused in a body, move towards the target and enters the nucleus.

Chromallocytes are ideal for gene replacement, provide a sustained cure for all genetic disorders. It would provide 100% efficient and complete cure.

Chromallocyte structure

Chromallocyte is a lozenge-shaped structure having the surface area of 102.778 microns. It has

estimated an external volume of 69.250 microns. This nanorobot is 4.18 micron in width, 3.28 micron tall an and 5.05 micron in length.

Manipulator

The manipulator is axially placed on the surface of nanorobot. This manipulator is known as proboscis manipulator. This manipulator collects the faulty material i.e chromatin from cell and transfers new one from the interior of robots. These proboscis manipulators are same as that of telescopic manipulators but the only difference is the proboscis contains no telescopic joints. It is made up of rotating joints arranged in a way that the rotation makes change in angle of the manipulator during functioning. Proboscis contains smooth cylindrical structure and a hollow internal area which accommodate a chromatin payload. This also prevents the outflow and also an entry of external fluid into an interior[38-64].

Funnel assembly

After the Proboscis has spooled the nuclear chromatin into an ellipsoidal bolus, the funnel assembly is extended out into the nucleoplasm, surrounding and ultimately fully enclosing the bolus.

Chromatin storage chamber

The new chromatin to be delivered in the cell nucleus is carried by chromatin storage chamber. As soon as new chromatin is discharged, the old chromatin is forced into the storage vault[65,66].

Mobility assembly

Telescopic grapples are utilized for mobility. These grapples are ~2.5 times that of the telescopic manipulator. These grapples are relatively short as compare to robotic dimension but has adequate ability to walk on the vascular and cellular surface which are covered with a glycocalyx (10-100nm thick).

Power source-the 10 acoustic power receiving units are placed at equal interval which will supply energy to nanorobots[66-76].

Ex vivo chromosome sequencing

The new set of chromosome sequence which is to be placed in the defective cell is manufactured ex-vivo. For this purpose, cellular chromosomes set from a patient is taken for genome sampling and modification and chromatin are synthesized.

Working of chromallocytes

The entire process of chromosome replacement therapy takes around 7 hrs.

Organ survey for targeting

The chromallocytes are placed in or around the patient's target organ. To drive the chromallocytes near the target organ, a navigation system is utilized. This process requires around 1 hr time.

Chromallocyte preparation

The chrmallocytes are manufactured according to the type of function to be done. These chromallocytes are loaded with the new set of chromatin to target each individual cell. Approximately 1012 chromallocytes and the process takes 1hr.

Patient preparation

Patients to be subjected to this treatment are placed on the ultrasonic vibrating table with acoustic power transmission into the body. This will provide energy to chromallocytes activity. Respirocytes are also injected in this process which carries oxygen[77].

Flexible nano cannula is injected near or around the target organ to provide the path for the entry of chromallocytes.

Injection

The nanorobots are injected through the nano cannula which is inserted neat the target organ. The structure is like transdermal[78] microcannula[79,80].

The chromallocytes starts flowing through the blood and navigate the target organ through navigation grid and reaches to the capillary bed near target cell.

Extravasation

In this, the nanorobot passes out of tissue in the surrounding area.

ECM immigration

Chromallocytes proceeds through the extracellular matrix (ECM) and moves towards the target cell. This is done using mechanical mobility system for histonation. Chromallocytes passes by 100 micron/sec through ECM.

Cytopenetration

Chromallocytes penetrates through the cell membrane of a target cell. The Salvation wave drive

mechanism is used for the penetration. Mobile grapples and movable semaphore binding site together facilitates the membrane contact and penetration.

Block mechanotransduction

Chrmallocytes breaches the cellular membrane which transmits the signal which alters the gene expression. These nanorobots have weak signal but for longer duration which may cause mechanotransduction. To block this mechanotransduction process, nanorobots are released with cytosol engineered transduction inhibitors according to cytotype of a target cell[81,82].

Nuclear localization

Once inside the cell, chromallocytes containing semaphore get exposed to an anterior surface of a cell. This binds with the outer nuclear membrane surface.

Nucleopenetration

This is carried out by utilizing enzymatic end effectors which are analogous to cellular protein kinase C. This protein kinase has the ability to phosphorylate and locally dissolve the nuclear lamina (the process as performed by cytomegalovirus)[83]. Further, it makes cut in the INM (Inner Nuclear Membrane), permits the entry of chromallocytes.

Block cell apoptosis

The action on cell is considered as chemical[86] or mechanical[84,85] destruction of cell. Hence the cellular response get triggered. Removal DNA triggers the cell apoptosis. Hence the blocking of this activity is necessary. This is achieved by releasing artificial caspase inhibitor which will stop the cell suicide.

Blocking of DNA repair

The entry and the activity of chromallocytes is something which is not according to the natural mechanism. Hence it is considered as damage to a cell. This will activate the sensing mechanism. Disruption of double-stranded DNA activates the signalling cascade. To block this normal cell behaviour, chromallocytes blocks DNA repair response by inhibiting ATM inhibitor.

Block inflammation

Cell damage releases signal molecules like the chromatin-associated high mobility group box1 (HMGB1) protein that binds with high affinity to RAGE (the receptor for advanced glycation end products). These act as mediators of inflammation. Hence in the chromallocyte activity, this must be blocked. Chromallocytes block this inflammatory response by either releasing phosphatase inhibitor or by engineered enzyme bearing precise identification of HMGB1[87,88].

Deactivate transcription

The DNA transcription is the process in which enzyme RNA polymerase attaches to the DNA strand and starts the production of complementary RNA. To block this process, the chromallocyte can release into the nucleoplasm an appropriate engineered molecules analogous in action to reversible transcription inhibitors such as the adenosine analogue 5, 6-dichloro-beta Dribofuranosylbenzimidazole (DRB), alpha-amanitin, or actinomycin D (AMD)[89].

Detach chromatin

By the process of blocking cell apoptosis and cell response pathway, the cellular anaesthesia is produced. Hence it is easy for the chromallocyte to reach chromatin from INM (Inner Nuclear Membrane).

Lamin B which is a part of an apoptotic cascade is the enzyme which is cleaved by lamin protease enzyme. This cleavage allows the detachment of chromatin from the surface[90].

Extend proboscis

Extention of proboscis provide adhesion surface to which chromatin will attach.

Rotate proboscis

Proboscis has 2 rotation 1. Co-axial- This rotation wind the chromatin fibres around a shaft of a manipulator. 2. Lateral gyration- this will allow access to the nuclear interior. Chromatin wind and drawn inward and coiled.

Deploy funnel

Once the proboscis coils a chromatin, manipulator is moved to co-axial position and stop the rotation. Funnel assembly starts extending outwards and

applies appropriate cutting force to break stray chromatin. After the completion of this process, the assembly gets sealed and all the proboscis is retracted. Surface chromophilicity is switched off.

Digestion of stray chromatin

The collected stray chromatin is digested in vivo in this step. If any stray chromatin remains as such, chromallocyte releases an engineered DNA nuclease that can digest stray chromatin[91,92].

Insertion of new chromatin

The proboscis manipulator has two functions. One of which is the discharge of new chromatin. The new set of chromatin is released into nucleus by proboscis. Chromatin passage through a micropipette does not appear to damage it and core histones do not separate from DNA even when chromatin is subjected to extreme stretching[93].

Reactivate transcription

As the new chromatin is dispensed, a cell should gain back its original functions. To reactivate the transcription process, the chromallocyte must acquire transcription inhibitors. This process is carried out by using sorting rotors which contains a binding site for inhibitors.

Remove nuclear blockade

Engineered inflammation signal inhibitors or enzymes released are reacquired by the chromallocyte, and blockage of DNA repair and apoptosis pathways is reversed by extraction of relevant factors using molecular sorting rotors. The Proboscis is fully retracted to its original interior position.

Reverse nucleopenetration

The chromallocyte will be slowly withdrawn from the nucleus. The breached surfaces formed are self-sealed by a simple gene mutation which will cover nuclear pore openings[94]. The endoplasmic reticulum (ER) can provide new material to fill holes formed in the process[95].

Reverse cytopenetration

The chromallocytes are withdrawer from the cell by passing through the cell membrane into the extracellular region. The plasma membrane is sealed[96] by using fusogens[97,98]. Simultaneously, the mechanotransduction mechanism is regained by retrieving the synthetic inhibitors.

ECM emigration

In this step, the chromallocyte will proceed towards the nearest capillary vessels.

Reverse transmigration

For the exit, chromallocytes pass through tissue by extravasation via basal to apical transendothelial migration. Then get entry into the vascular lumina. Again the breached surfaces are resealed[99].

Exit from body

Nanocannula which is used for the injection of chromallocytes, is again used for the exit through the body. Previously obtained navigational pathway and navigation map is used to search for exit gate i.e cannula.

Another way of exit is through renal tubule or phagocytosis.

Nanorobots in tissue reconstruction

Nanorobots containing nanoparticles can be employed in reconstructing bone structure. The nanorobots are constructed similarly to the bone structure. Ultrasound is used in the process of bone reconstruction. Ultrasound gives the pictures of muscles, joints, tendons and ligaments throughout the body. Ultrasound helps to diagnose tears, strains and soft tissue conditions. Hence ultrasound imaging is used in nanorobotic treatment. According to the pattern obtained in ultrasound, nanostructures are prepared. These bone-like structures are inserted inside the body using nanorobots. When these nanoparticles containing nanorobots reaches the fractured bone, they assemble itself. The arrangement is made such that it will form a bone-like structure which will later become a part of bone. Hence, these kind of nanorobots can be used in bone fractures and arthritic situations[37].

Nanorobots in kidney diseases[100]

Nanoscale engineered advances will permit manageable and controllable devices which can be employed in kidney problems. The nanoscale devices are designed such that it will be compatible with kidney cells and other structure. For this understanding of chemical and physical properties

of kidney cells and tissue is necessary. These must be studied at the atomic level. Advanced approaches can be utilized to overcome major kidney diseases.

Presently, kidney stones are destroyed using Extracorporeal Shockwave Lithotripsy, Percutaneous Nephrolithotomy, Ureteroscopic Stone removal are some of the treatments used to destroy kidney stones. But these treatments have some drawbacks like pain and other side effects. The use of shock waves converts stones into the sand like material which increases the risk of diabetes and high blood pressure. Hence the effective treatment is necessary to carry out this process. Nanorobots could be able to destroy kidney stones using the laser. Nanorobots containing small ultrasonic signal generator will deliver frequencies to stone and break it. These small particles will be excreted through urine[101].

Gout

Gout is a result of a condition known as hyperglycemia. It is a situation in which uric acid crystals get deposited in joints.

Gout is a condition in which uric acid crystals get deposited in joints. Gout results from the hyperuricemia condition. In such circumstances, kidney looses its ability to remove waste from the breakdown of fats from bloodstream. These gets deposited in joints like knees and ankles. People with this situation suffers from intense pain.

Nanorobots can help in breaking up these crystals and provide relief from the symptoms. But this technique would not be able to reverse the condition permanently[102].

Parasite removal[102]

Combining several nanorobots together can be used for destroying parasites[103].

CONCLUSION

Use of nanorobots in medical application will provide a wealth of promise. Nanotechnology in various fields faces many challenges. The use of nanorobots in drug delivery will lead to faster relieve. The cure for a particular disease will be convenient and easy. The therapy using nanorobots will reduce the side effects significantly. Critical surgeries can be avoided and done with lesser pain to the patient.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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