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Nanorobot – A Prospective Outlook in Medicine

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Abstract

Nanorobotics is an emerging field based on the principle of nanotechnology. It deals with design and construction of devices so as to alter their functioning at the atomic, molecular or cellular level. Dr. Robert Freitas has designed nanorobots like clottocytes, respirocytes and microbivores. These hypothetical nanorobots are very small in size which can easily travel into human body and perform their functions. These nanorobots are designed in such a way so as to perform functions under specific conditions inside a human body. These nanorobots act as artificial substitutes to blood. The clottocytes mimics the process of haemostasis. The respirocytes mimics the function of red blood cells of transporting oxygen and carbon dioxide to various tissues and cells of the body. The microbivore mimics the function of natural phagocytes, which is carrying out phagocytosis. This review paper will discuss how the recent advancements in nanorobotics have helped in designing of these nanorobots.

Keywords: Nanorobot, Nanomedicine, Clottocytes, Respirocytes, Microbivores

Introduction

The engineering and manufacturing at the molecular level is termed as nanotechnology. Using this nanotechnology to formulate medicines is called Nanomedicine. These Nanomedicine which work to deliver medicine for the purpose of diagnosis, mitigation , prevention and cure can also be termed as nanorobots [1]. Nanotechnology involves manipulating the matter at the nanometer level and applying this principle to the medicine is called Nanomedicine [2]. The scope of Nanomedicine is very vast. Principles of Nanomedicine could be explored to make devices that can work inside a human body at molecular level leading to improvement and maintenance of human overall health [3]. The major challenge today is to overcome the hurdles that are causing hindrance in its applications in various fields. With proper knowledge about pathophysiology of the disease and the molecular working of the nanorobots, scientists and engineers can develop nanorobots which can efficiently treat most of the incurable diseases, responsible for many deaths all around the world [4]. Recently a lot of development in this field is taking place. Many scientists have designed a model for treating and diagnosing various diseases in the fields of neurology, dentistry, oncology, cardiology and other medical fields. With advancement in designing various models focusing on various diseases, need for studying or designing it's in vivo characteristics is also necessary. Apart from *in-vivo* studies, need for toxicity studies are also important. A screening strategy for evaluation of different engineered nanomaterials is given by Glunter Oberdorster et al. [5]. There are no guidelines for the effective and safe use of nanomedicines as given by the FDA. But looking at the pace with which developments are being carried out in this field,

FDA soon will come up with the approval and guidelines for nanomedicnes. Looking at the recent advancements in the field of Nanomedicine and nanotechnology, we can foretell that nanotechnology most likely be called as "the next industrial revolution"[6]. In this review I have covered the study of three nanorobots designed by Dr. Robert Freitas.

Traditional therapy for blood coagulation and problems associated with it

Blood loss is incurred is many diseases like Hemophilia, Afibrogenemia, Vitamin K deficiency, hemolytic anemias, liver diseases, deficiencies of factor VIII, IX, XI and other diseases [7]. Apart from this blood loss can also happen due to accidents or during a surgery [8] and in post-partum hemorrhage [9]. The coagulation cascade system of our body is responsible for the coagulation of blood. However due to lack of some deficiencies like vitamin B12 deficiency or aplastic anemia, this cascade might take long time to coagulate blood resulting in fatal blood loss [7]. Blood loss can be treated by restoration of lost blood, achieving blood coagulation or treating the source of bleeding. Blood component therapy is used to treat blood loss by giving blood of compatible blood group to the patient. In case of emergency, obtaining blood of compatible group is very difficult. Loss of other blood components like platelets, plasma can be restored by transfusing platelets and fresh frozen plasma or cryoprecipitate. While carrying out this transfusion, it is very important to maintain the critical level of blood in a patient [10]. Blood loss can also be treated with antifibrinolytic agents. Antifibrinolytic drugs like tranexamic acid, aminocaproic acid, aprotinin and aminoethyl benzoic acid can be used to promote blood clotting and preventing the breakdown of blood clots formed [11]. However, there are side effects related to antifibrinolytic agents as well. Tranexamic acid is associated with increase in the thromboembolic events due to its mechanism of action. [12].

Clottocyte: A novel solution to traditional problem

To overcome various problems faced while treating blood loss, Dr. Robert Freitas has designed a nanorobot called clottocyte. Clottocyte is a theoretical model designed by Dr. Robert Freitas Jr. Clottocytes is artificially working mechanical nanorobots which work on the principle of platelets. They would bring about effective hemostatis in 1 second. They are designed of the same size as that of natural platelets i.e. 2 microns. Due to its small size it can efficiently operate at cellular level without the danger of blocking any blood vessels. Clottocytes work on the power of serum oxyglucose and are controlled by onboard computers. They are composed of fibre mesh. These meshes are biodegradable and covered with soluble coating over specific areas of the mesh. The soluble coating would dissolve when it comes in contact with plasma and form a sticky mesh. The stickiness is blood group specific which would help in trapping specific antigen carrying the red blood cells. The mesh on adherence to blood vessel will be able to unfold near the site of injury. The neighboring mesh would be attracted towards the mesh near injury and immediately bleeding will stop [13].

Challenges

However, there are some challenges that need to be overcome.

1. Designing of special control procedures is needed to make sure that clottocytes do not release their mesh in the unwanted place inside the body or at wrong time.
2. Several other controls with respect to sudden shifts in pH and ionic concentration need to be monitored.
3. The mechanical action of clottocytes is very rapid while the inherent blood coagulation process is slow which might disturb the normal equilibrium. Various chemical substances might be added to clottocytes which will be necessary to ensure normal working of coagulation cascade.
4. While assisting internal sealing of a vessel, clottocyte might cause blockage of lumen.

They offer effective advantages over the challenges. They are 100-1000 times faster than the natural hemostasis. To initiate a coagulation cascade 1-300 platelets are required but in contrast only one clottocyte can effectively detect vessel lesion and ensure quick communication to the neighbors thus enhancing the coagulation process. Only ~0.01 % of concentration of cells is required to carry out efficient clotting. Hence clottocytes can be said to be approximately 10,000 times faster than the natural platelets. Clottocytes sounds as a novel blood clotting procedure as compared to traditional therapies which involves critical controls and danger to patient's life.

Traditional solution for oxygen deficiency and problems associated with it

Hemoglobin is a respiratory pigment which carries high levels of nascent, molecular oxygen at 1 atmosphere pressure to all the tissues of our body. During blood loss, hemoglobin levels in the blood drop down. To provide continuous supply of oxygen to blood in absence of hemoglobin, oxygen is supplied to the body externally. When the hemoglobin level drop is severe, supplying of hyperbaric oxygen might be essential. Hyperbaric oxygen is supplied in colloid diluted intra-vascular fluids [14]. Hypoxia is the main indication of oxygen therapy. Hypoxia results from the lack of oxygen at the tissue level. Hypoxemia is a condition where the arterial oxygen tension is below normal levels. There are many conditions which causes hypoxia or hypoxemia [15]. Hypoxia is also observed in acute respiratory failure and pulmonary diseases. Higher concentration of oxygen needs to be supplied during acute respiratory failure. Oxygen is supplied in high flow rates via a cannula. The oxygen therapy needs to be continuously monitored with critical parameters like gas – exchange. Utilization of administered oxygen by the tissues must be ensured [16]. Pneumonias can cause severe hypoxemia resulting in acute respiratory failure. Oxygen is administered via a cannula with controlled flow rate [17]. Patients suffering from COPD often have hypoxemia. Respiratory tract infection often causes airway obstruction leading to worsening of hypoxia. To treat this aggravated condition, oxygen is required until normal condition is achieved [18]. A major pulmonary arterial embolism can induce hypoxemia. The lung gets devoid of arterial blood resulting in low delivery of oxygen at alveolar level. Oxygen therapy is required to supply alveolar oxygen [19]. Ischemic heart disease also results in hypoxia due to low level of oxygen in tissues and arteries. Hypoxia can cause breathlessness. This condition can be reverted by administering oxygen therapy. Oxygen improves cardiac muscle oxygenation and relives breathlessness. It also increases tissue contractility [20].

The oxygen therapy is a risky treatment with a lot of parameters to control while administering it. Some of the other problems associated with oxygen are mentioned below [15].

1. Oxygen supports combustion and therefore the oxygen tanks are at high risk to catch fire and explode. Smoking should be strictly restricted when in proximity of oxygen tanks. The oxygen tanks should be kept in room which is circulated with fresh air since accumulated gases may cause it to explode.
2. The cannula, masks, catheters which are used to supply oxygen might cause injury to nose and mouth.
3. In patients with COPD, there is risk of accentuating hypoventilation. This may include carbon dioxide narcosis called as hypercapnia. Carbon dioxide retention should be monitored with the help of pH as the parameter. Carbon dioxide retention should not result in acidemia [21].
4. Long term oxygen therapy might cause structural damage to the lungs. Proliferative and fibrotic changes due to oxygen toxicity have been observed [22].

Respirocyte: A novel solution to traditional problems

Respirocyte is the theoretical concept given by Dr. Robert Freitas. It is a nanorobot which behaves like red blood cells. It can be used to enhance or totally replace our red blood cells which perform the function of oxygen and carbon-dioxide transport. Hemoglobin is the natural pigment which transports oxygen and carbon dioxide all across the tissues. Respirocyte can work as an oxygen transporter with a potential capacity for oxygen 2366 times greater than hemoglobin. Respirocyte work on the principle of nanomolecules. It works at the molecular level. It has a diameter of 0.2-2 microns. It is made of diamond which was found to be biocompatible with the body [23].

Construction of Respirocyte

1. **Pressure vessel**: This vessel can be constructed from a biocompatible and strong material which can withstand the high pressure of the gases. Diamond and sapphire has been thought to be the most suitable material. It can be spherical, compact and microscopic. An optimum pressure of 1000 atmosphere is maintained so that the risk of rupture and energy explosion is avoided. The vessel is very densely packed. In comparison, red blood cells store oxygen at the pressure of 0.51 atmosphere pressure. The oxygen delivery through this vessel is continuous. The system can be made more sophisticated by making the oxygen delivery responsive to the local oxygen pressure. The duration of oxygen delivery can be extended by recharging the vessels with oxygen via the lungs. Carbon dioxide toxicity can be prevented by providing additional vessel for carbon dioxide which would actively transport the gas from all the tissues and unload it into lungs for exhalation. The vessels would be maintained properly so as to avoid acidifying of the blood. Respirocytes would generate less carbon dioxide toxicity as compared to red blood cells.

2. **Molecular sorting rotors**: The active delivery of gases in and out of the vessels is considered as successful working of Respirocyte. The active delivery of gases in and out of the pressurized vessels is carried out by molecular sorting rotors. Each rotor has a binding site which is exposed to the blood plasma. This rotor is connected to a rotation disc. Each pocket of gas selectively binds to the binding site when they are facing the plasma. When the rotation disc moves, the pocket is pushed by the cam of binding sites into internal chamber with high energy. These rotors are reversible so they can bind and unbind to the gas pockets and fill the vessels continuously.

3. **Sorting rotor binding sites**: The binding sites must have specific structural and functional receptors for different gases that might be transported through the rotor. These binding sites must have high affinity and specificity. They should be able to survive the long exposure to the blood.

4. **Buoyancy control using water ballast**: The maintaining of buoyancy in an aqueous media is very important. This can be controlled by loading and unloading of water ballast. Small sized Respirocyte settles slowly out of a suspension. Buoyancy is essential when the Respirocyte has to be removed out of the body after its purpose has been served. Onboard water ballast is extremely useful during this process. No other components of the blood can maintain buoyancy; hence they are precipitated outwards by centrifuging gently. They are carefully separated and added back to the filtered plasma on the other side of apparatus. After centrifuging, the plasma contains mainly Respirocyte and the other solid components of the blood. The Respirocyte are separated by filtering through 1

micron filter. Filtered plasma is recombined with the solid components of blood and re-administered to a patient undamaged.

Challenges

1. Device overheating might take place if it is deposited in a dry, non-aqueous area or when inbound sorting rotors lead to overloading of pressure vessels.
2. The circulating Respirocyte can interfere with the erythropoiesis. Respirocyte prevents hypoxia, which reduces the secretion of hormone erythropoietin. With reduction in levels of this hormone, erythropoiesis is suppressed. It can be possible to adjust the working of Respirocyte only when the red blood cells are stressed.
3. Continuous spinning or movement of the sorting rotors can cause damage to the blood components.
4. Cells larger than 1 micron are removed from the blood by the reticuloendothelial system. The kupffer cells of the liver are responsible for removing the cells from blood. If these cells identify the Respirocyte, it might lead to blockade of phagocytic system since Respirocyte are not metabolized.

Advantages

Despite the challenges, Respirocyte has various advantages:

1. Patients can be treated rapidly without any delay in case of traumatic conditions or serious accidents. The need for compatible blood group is also not essential.
2. Transfused blood and the transfusion process is very costly and risky. Respirocyte can act as good substitutes to blood.
3. Respirocyte are easy to store and maintain. They can be stored at room temperature without the risk of damage unlike blood and blood substitutes.
4. Respirocyte can act as an *in-vivo* scuba device. A person can dive in water without resurfacing for about 4 hours [24].

Solution to antibiotic resistance and problems associated with it

Antibiotic resistance is a clinical condition where the antibiotics are no longer effective in killing bacteria. The reason the bacteria develops this resistance is because it develops a mechanism which could resist the harmful attack by the antibiotics. The phenomenon of antibiotic resistance is rapidly spreading across the world. Spreading along with it are the antibiotic resistant bacteria. This has endangered the efficacy of antibiotics in killing the bacteria. These antibiotics were once transforming and saving millions of lives [25].

The antibiotic resistance has been attributed to a lot of causes like overuse, inappropriate prescribing, and extensive agricultural use of the antibiotics. Apart from this, unavailability of new antibiotics is also attributed for the cause of antibiotic resistance [26].

Methilcillin resistant *Staphyllococcus aureus* has been found to be resistant to all the β- lactam antibiotics [27]. Mycobacteria tuberculosis has been found to be resistant to a number of drugs used for the treatment of tuberculosis. It is resistant to the first line drugs like isoniazid, rifampicin, pyrizinamide, ethambutol and second line drugs like capreomycin, amikacin, kanamycin and fluroquinolones. Resistance to so many drugs has led to failure in treatment of tuberculosis. *Pseudomonas*

aeruginosa is resistant to drugs like cephalosporins, carbapenems, aminoglycosides and fluoroquinolones. *Neisseria gonorrhoeae* is resistant to drugs like cephalosporins, penicillins, fluroquinolones and tetracyclines [28].

Spreading of antibiotic remittance can be controlled by reducing the use of antibiotics in agriculture and food animals. The problem of antibiotic resistance can be controlled by preventing the flow of resistant genes from animals to the humans. One more strategy is to strengthen the immunity system by various means like vaccines, good hygiene, probiotics and prebiotics, antibacterial peptides from natural sources as a substitute to antibiotics. Various novel strategies should be introduced to *invirogate* the process of antibiotic development, so as to ensure continuous availability of new methods to combat antibiotic reistance [29].

A lot of scientists have come up with novel strategies like the bacteriophage therapy, combination therapy, nanotechnology involving the use of various metals in nanosize, herbal substitutes and many more. However, these strategies have not led to complete eradication of antibiotic resistance. They can only control the spread of antibiotic resistance upto certain level.
Therefore, invention of a novel strategy that can skillfully kill the smart bacteria is needed. Microbivore also called as artificial mechanical phagocyte is a device skillfully designed to kill all the species of bacteria. It is a theoretical concept designed by Dr. Robert Freitas and it sounds like a perfect solution to the ever-growing problem of antibiotic resistance.

Microbivores: A novel solution to antibiotic resistance

Microbivores is a collective term which includes many types of medical nanorobot for use in a wide range of antimicrobial therapeutic conditions. Microbivore is a simple device which is administered intravenously and functions on the principle of natural macrophages. Their primary function is phagocytosis by using 'digest and discharge' protocol. It can rightly be called as mechanical phagocyte or artificial phagocyte [30].

The microbivore is an oblate spheroidal shaped device. It has 610 billion incisively arranged structural atoms with enough space for 150 billion atoms that will bind when the device is fully loaded. The diameter of the major axis of the nanorobot is 3.4 microns and that of minor axis is 2 microns. The diameter is less than that of natural phagocytes of 4 microns. A small diameter size ensures that the microbivore can pass readily through the blood vessels in the body without clogging. It has a volume of 12.1056 microns$^{3.}$ The device requires upto 200 pW of continuous power supply while in operation. It can completely digest a microbe at the input rate of 2 microns^3 per 30 sec cycle.

During each cycle, the target bacteria gets bind to the binding sites which are reversible and site specific. Telescoping grapples then emerges and secure anchorage onto the bacteria's plasma membrane. The telescoping grapples then pushes the bacteria into the ingestion port. Through ingestion port it passes into the Morcellation chamber where the bacteria are minced to small fragments with the help of blades. An ejection piston then forces the minced fragments into digestion chamber. The digestion chamber contains pre-engineered enzymes. These enzymes digest the fragments into mono residues which are harmless. The mono residues like glycerol, free fatty acids , simple sugars are formed which do not initiate any allergic cascade. These mono residues are then discharged from the device via an exhaust port which is at the rear of the device. This completes the cycle of 30 seconds. This process is called as digest and discharge protocol.

The detailed specifications and working of the various components of microbivore is discussed below:

1. **Reversible microbial binding sites**: the very first function the microbivore perform is to attack the bacteria by binding to it. The collision of the bacteria and the microbivore leads to intimate contact of the surfaces of the both. During this, the bacteria are recognized by the binding sites. After the bacteria are recognized, it binds to the binding sites reversibly. Recognition of the bacteria is important since, all the bacteria can't bind to same binding site. The bacteria are often distinguished based on their cell membrane. The gram-negative bacteria have different markers than the gram-positive bacteria. A trimeric channel protein called porin is present in the membrane of *E. coli.* Mycobacteria contain mycolic acid in their cell membrane. The outer membrane of the bacteria contains amino acid which are right handed on contrary to left handed amino acids present in our body. These right handed amino acids are not susceptible to the digestive enzymes of our body.

   A microbivore should be able to distinguish between 500 different bacterial species. Each bacterial cell can be identified by using approximately 9 antigenic markers. Each receptor block consists of nine 7 nm * 7 nm of receptor sites. There are 20,000 such receptor blocks. A single receptor accounts to produce a binding force of 40-160 pN.

2. **Telescoping grapples:** once the target bacteria is recognized and temporarily bound to binding sites, telescoping grapples emerge from the microbivore and secure anchorage onto the bacteria's plasma membrane or outer coat. The telescoping grapples have pressure sensors on their surface to help distinguish between gram negative and gram positive bacteria. This helps in confirming the identity of the bacteria. The telescoping grapples are operated by the elevator mechanism. The grapples are enclosed into subgrapple chamber into which compressed nitrogen is rotored in or out. This gas helps in moving the pneumatic piston which controls the extension or retraction force required by the telescoping grapples. Each grapple is terminated by a reversible footpad of 20 nm diameter. For gram positive bacteria, the footpad consists of 100 closely packed lipophilic binding sites which bind to the lipid molecules in the plasma membrane. For gram negative bacteria, the footpad has binding sites consisting covalently attached transmembrane protein molecules which are linked to murein. The footpad can be rotated with the help of internal pull cables. This avoids the adhesion of bacterial slime. There is one grapple per 0.09 micron^2 of nanorobot surface. After the telescoping grapples pass on the bacteria into ingestion port, they are free to maneuver other pathogens as required.

3. **Ingestion port and Morcellation chamber:** the ingestion port consists of a door which is oval shaped and works on the mechanism of irising. They provide an aperture of 1 micron^2 when fully opened. If the viruses need to be securely allowed into ingestion n port, the door can mechanized to work in an off centre manner. If the bacteria are as large as 6 microns, they can be ushered into the ingestion port by door opening at the centre. Opening of ingestion port leads to entry into Morcellation chamber. Morcellation chamber is a cylindrical chamber with a length of 2 microns and volume of 2 microns.

   The chamber has 10 diamondoid cutting blades. Each of the blades is ~2 micron long, ~0.25 micron wide, 10 nm thick and offering a cutting edge of 1 nm. These blades have alternate chopping geometries so as to completely

mince the bacteria from all the angles. Other such mechanism used for mincing could be a diamondoid sieve which would sieve the bacteria. Once the bacteria are minced into fragments, they must be transported to digestion chamber. This is carried out by the ejection piston. The door separating the Morcellation chamber and Digestion chamber must be opened before activating the piston. The piston can also be used to carry the material from the ingestion port into Morcellation chamber. Apart from piston mechanism, vacuum is also provided to pull the material into the chamber.

4. **Digestion chamber and exhaust port**: The digestion chamber has the same volume as that of Morcellation chamber, i.e. 2 microns^3. Digestion chamber is cylindrical cross-section oval shaped chamber surrounding the Morcellation chamber. It is 2 microns in width, 1.3 microns in height and 2 microns in length. Digestion chamber contains preprogrammed sequence of engineered enzymes. After the bacterial fragments are pumped into digestion chamber, they are digested by the enzymes into monoresidues like amino acids, free fatty acids, monosaccharide and mononucleotides. These mono residues are discharged into the blood via the exhaust port.

Challenges

1. Microbivore can be trapped by the phagocytic cells considering that it is foreign particle. Thus it may undergo phagocytosis. This can be solved by the use of phagocyte engulfment inhibitors.
2. The bacteria with the flagella should be carefully and fully internalized. If not, the flagella might be left into the blood. These flagella are antigenic and could trigger an allergic response.
3. The engineered enzymes present in the microbivore can get partially degraded after which they could be ejected into the bloodstream. After entering into bloodstream, they may show immunogenic, inflammatory and any other harmful activity. The microbivore enzymes should be designed such as to enable their digestion by the natural enzymes present inside the body.

Advantages

1. Microbivore are ~1000 times faster than the natural phagocyte or antibiotic assisted phagocytic defense mechanism.
2. They are ~80 times more efficient as compared to natural phagocytes.
3. Natural phagocytes release bioactive compounds during the phagocytosis process. Microbivore on the other hand release biologically inactive fragments which do not trigger any immunogenic response.
4. Apart from their use in humans, they can be used in veterinary and military applications.
5. Their working can be explored for various applications like sterilization of food products, cleaning of biohazards, treatment of biopolluted drinking water and many others.

Conclusion

Use of nanorobots has been explored in various fields of medicine. These nanorobots serve the purpose of maintaining and protecting the human body. Serious medical treatments which require the control of many critical parameters can be easily performed by the use of nanorobots. These nanorobots are predicted to provide a wealth of promise. Considering the severe effects of the existing therapies involved in the treatment of serious diseases and conditions nanorobots are found to be more innovative in treating vital diseases. Few challenges currently exist in the designing and working of nanorobots, but with the

advancements in technology scientists will very soon find solution to these problems. The use of nanorobots can be explored in various diseases like cancer, AIDS, heart attack and so on. Very soon the nanorobots would be seen replacing the existing therapies for various conditions and very rightly it will be the next industrial revolution.

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