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Nanorobotic Applications in Medicine: Current Proposals and Designs

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Abstract

Advances in technology have increased our ability to manipulate the world around us on an ever-decreasing scale. Nanotechnologies are rapidly emerging within the realm of medicine, and this subfield has been termed nanomedicine. Use of nanoparticle technology has become familiar and increasingly commonplace, especially with pharmaceutical technology. An exciting and promising area of nanotechnological development is the building of nanorobots, which are devices with components manufactured on the nanoscale. This area of study is replete with potential applications, many of which are currently being researched and developed. The goal of this paper is to give an introduction to the emerging field of nanorobotics within medicine, and provide a review of the emerging applications of nanorobotics to fields ranging from neurosurgery to dentistry.

Keywords

Surgery; nanorobotics; nanomedicine; NNI; magnetotactic bacteria

Introduction

Progression in science and medicine has been marked by the ability of researchers to study and understand the world around us on a progressively smaller scale. With each order of magnitude of access to smaller dimensions, new therapeutic possibilities and frameworks of understandings were developed. These developments included the germ theory and microbiology

The next phase in the ever-decreasing size of operation is the development of nanotechnology, where researchers are able to work on the scale of nanometers. The scale of nanotechnology is defined by the National Nanotechnology Initiative (NNI), a United State government initiative to promote the development of nanotechnology research and development, as “science, research, and technology conducted on the nanoscale.” The NNI defines this scale as approximately 1 to 100 nanometers. To give a practical idea of the

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nanoscale, a cell surface receptor is approximately 40 nanometers¹, a strand of DNA is about 2 nanometers in diameter, and a molecule of albumin is about 7 nanometers.

To date, some examples of what nanotechnology has enabled include the development of improved imaging techniques for higher sensitivity in detection of cancer and illness², improved targeting of drug treatments³, decrease in the number of adverse effects of chemotherapy, and the enhanced effectiveness of other antineoplastic therapies such as cryotherapy⁴ and ultrasound⁵. Outside of medicine, nanotechnology is also fueling developments in agriculture⁶, energy⁷, electronics⁸, and many other fields.

The concept of nanotechnology is reported to have first been envisioned by the celebrated physicist Dr. Richard Feynman, during a lecture called “There's Plenty of Room at the Bottom,” which was delivered to the American Physical Society in December of 1959. Dr. Feynman discussed the field and scale of nanotechnology in principle, and the possibilities it would unlock for biological research, information technology, manufacturing, electrical engineering, and other fields⁹.

Nanobiotechnology is a subfield of nanotechnology that uses the principles and techniques of nanotechnology and applies them towards research and advancement in the biological sciences and medicine. Nanobiotechnology involves the development of technology such as pharmaceuticals and mechanical devices at the nanometer scale for the study of biological systems and treatment of pathology¹⁰. This article will focus on the advances of nanobiotechnology in the realm of device development, specifically on the construction of nanorobotics and their application in the medical field. Representative examples from the fields of microbiology, hematology, oncology, neurosurgery, and dentistry will be reviewed.

Microbiology

The field of microbiology has been successfully used as a springboard for the initial development of robotic functions in nanobiotechnology. Although microrobots and nanorobots can be constructed and have function¹¹, their use within the vascular system is limited by challenges with transportation and propulsion. An effective strategy for enabling propulsion of microrobots and nanorobots is coupling them to magnetotactic bacteria such as *Magnetococcus*, *Magnetospirillum magnetotacticum* or *Magnetospirillum magneticum*^{12, 13}. The largest component of these nanorobots integrated into magnetotactic bacteria would be the bacterial cell component. The smallest known species of magnetotactic bacteria is the marine magnetotactic spirillum, which is 0.5 μm (500 nanometers), just above the upper limit of the NNI's definition of the nanoscale¹⁴. However, the marine magnetotactic spirillum's usefulness is limited by their speed, and magnetotactic cocci are more useful for intravascular function¹⁴.

The magnetotactic bacteria can be guided in the desired direction using the application of magnetic fields¹⁵. The components of the magnetotactic bacteria that are responsive to the magnetic field are called magnetosomes. Magnetosomes are prokaryotic pseudo-organelles with about 15-20 magnetite crystals, each about 50 nm in diameter, contained within an invagination of the prokaryotic cell membrane¹⁶. Magnetite crystals are composed of Fe_3O_4 .

a common iron oxide. Magnetotactic cocci have been found to travel in consistent and predictable patterns following established geomagnetic lines¹⁷.

There are several theorized practical uses to the development of such a device. A highly customizable structure can be ligated to the bacteria, containing therapeutic compounds such as pharmaceuticals and artificial antibodies for function at the target site¹⁸. There is also the potential for use of these device to collect information and function as sensors¹⁹. Larger robots have higher ability to function in and navigate through larger vessels with limited function in capillaries and small vessels. Smaller nanorobots are highly useful in capillary environments and the microvasculature, but cannot achieve high enough velocities for control in large vessels. A two-component robotic system including a larger system for transport and control through large vessels, followed by release of the smaller component into small vessels has been proposed, and is a promising idea for pursuing practical development this field²⁰.

Hematology

There is a rich base of research and potential applications for nanomedicine and nanorobotic applications in the field of hematology. From uses ranging to emergency transfusions of non-blood oxygen carrying compounds to restoring primary hemostasis, there is a wide array of applications under study for nanorobotics in hematology²¹.

One of these devices currently under design is a nanorobot dubbed a respirocyte. This robot is equipped to have three functions as it travels through the bloodstream. First, collecting oxygen as it passes through the respiratory system for distribution throughout the bloodstream. Second, collecting carbon dioxide from tissues for release into the lungs. And finally, metabolizing circulating glucose to power its own functions²². The total size of the robot would be about one micron, or 1,000 nanometers. However, the contained components would be constructed on the nanoscale. These include an onboard computer of 58 nm diameter, and oxygen and carbon dioxide loading rotors with a maximum 14 nm diameter in any one dimension²². The respirocyte is designed to carry 236 times more oxygen per unit of volume compared to red blood cells²². Development and use of this technology could provide an effective and lower risk alternative to blood transfusions.

The process of hemostasis is another area where nanorobotics may have applicability. Hemostasis is a sophisticated process involving several steps with a number of promoters and inhibitors balancing thrombosis and fibrinolysis²³. When hemostasis works appropriately, it can be very effective in halting bleeding and promoting vessel repair. However, there are natural limitations to physiologic hemostasis, such as an average bleeding time of about five minutes²⁴, that can be improved upon by nanorobotics. Additionally, when there is an impairment of our physiologic hemostatic mechanisms, such as with thrombocytopenia, our current methods of correcting this impairment have inherent risks. Patients undergoing platelet transfusions risk infection with pathogens and the potential of triggering an immune response²⁵. The proposed nanorobot for this function has been termed an artificial mechanical platelet, or “clottocyte”²⁶. The potential design parameters for this device have been described as a two micron nanorobot, containing a

mesh as thin as 0.8 nm and inundated with hemostasis promoting proteins, which is fired at areas of vessel injury to carry out hemostasis²⁶.

Finally, another potential use of nanorobots in this arena is as phagocytic agents²⁷. These nanorobots have been termed “Microbivores.” These robots would be designed to have a large number of customizable binding sites on their external surface, for antigens or pathogens for anything from HIV to E. Coli²⁸. Microbivores are theorized to be as much as 80 times more effective than our physiologic phagocytic capabilities, and could have the potential to clear septicemia within hours of administration²⁹. With the alarming rise in antibacterial resistance, developing nanorobots capabilities to battle infection may open promising avenues for treatment of infection.

Dentistry

A field in which nanorobots can have significant routine and specialized use is the field of dentistry. Virtually all the elements of dental care and treatment could incorporate nanorobots and benefit from their use by providing a higher level of care. These uses range from a routine cleaning, to cosmetics and teeth whitening, hypersensitivity, and even orthodontics³⁰.

Nanorobots can be incorporated into almost every aspect of dental care, including the initial analgesia a dentist may give at the start of a visit. A suspension containing millions of nanorobots is administered orally to the patient³¹. These robots are small enough to enter the gingival sulcus, and eventually travel through the micron sized dental tubules to reach the pulp³². Central control of these nanorobots would allow activation of analgesic activity in highly specific areas in proximity to where the dentist will be providing care³³.

Use of nanorobots in procedures such as root canal fillings or in the treatment of infection is also plausible. As discussed earlier, nanorobots can be enveloped in highly specific proteins to bind the targeted pathogens for the treatment of infection. For a procedure such as a root canal, the use of a tiny camera can provide visualization of the root, reducing any guesswork. Nanorobots can potentially increase the success rate of root canal procedures. In 2011, the National Health Service had a 70% success rate for root canal procedures, which leaves plenty of room for improvement³⁴.

Nanorobotics also has some potential function for the treatment of dental conditions such as dentine hypersensitivity. Studies have found that hypersensitive teeth can have significantly increased numbers of dentinal tubules compared to normal teeth, with the dentinal tubules also having a larger diameter than normal³⁵. Penetration of nanorobots into these dentinal tubules, with selective ablation or occlusion of tubules within the hypersensitive teeth would prevent stimuli from penetrating and inducing a pain response³⁶.

Other potential applications of nanorobotics in dentistry range from tooth repositioning via direct manipulation of periodontal tissues, dental cosmetic work via the direct replacement of enamel layers, or even nanorobots incorporated into a mouthwash or toothpaste where they would enhance daily dental care³². Nanorobotics has a wide array of potential applications to dentistry, and holds much promise as an area of development.

Neurosurgery

Nanotechnology has progressed from a theoretical proposal to a rich area of proposals and ideas, and now is an active area of practical research and developments. As a field that frequently functions on a microscopic level, neurosurgery is uniquely suited to benefit from many of the innovations nanotechnology has to offer. These benefits include improved detection of pathology, minimally invasive intracranial monitoring, and pharmaceutical delivery, amongst many others³⁷. The increase in our ability to work on an ever-decreasing scale has been greatly accelerated by advances in manufacturing microelectromechanical systems. These advances may allow manipulation on the scale of individual cells, and potentially on the molecular scale in the near future³⁸.

The topic of spinal cord injury and nerve damage is an important area of concern within neurosurgery as a field, and as a significant life-altering event for affected patients. The practice of reconnecting transected nerves has been done for more than 100 years, with progressive advancement in technique and technology. Currently, there are several different routes being pursued with the goal of optimizing and improving nerve reconnection outcomes, including promoting the regeneration of axons via growth factors³⁹ and enriched scaffolds⁴⁰. Restoring connectivity to transected axons is an integral step to the restoration of function. The ability to do this is limited by technical limitations to surgery on that scale⁴¹. Advancements in technology have led to the development of devices on the nanoscale which allow manipulation of individual axons. A nanoknife with a 40 nanometer diameter has been developed and found to be effective for axon surgery⁴². The use of dielectrophoresis, which involves the use of electrical fields to manipulate polarizable objects in space, has been found to be effective in achieving controlled movement of axons within a surgical field⁴³. Following controlled transection of axons and maneuvering them into position using dielectrophoresis, fusion between the two ends can be induced via electrofusion⁴⁴, polyethylene glycol⁴⁵, or laser-induced cell fusion⁴⁶, amongst other methods. Nanodevices are enabling a new dimension of precision and control with the reconnection of nerves.

One of the most effective ways to prevent morbidity and mortality in the field of neurosurgery is the treatment of cerebral aneurysms before rupture. Rupture of a cerebral aneurysm yields a high mortality rate. Ten percent of patients die before reaching the hospital, another 25% die within 24 hours of aneurysm rupture, and almost 50% die within 30 days⁴⁷. There have been no cost-effective guidelines determined for screening patients for cerebral aneurysm. Nanorobotics can present a potential option for screening for a new aneurysm, or closer monitoring of an identified aneurysm. Cacalcanti et al have proposed a design for an intravascular nanorobot with the capability to detect aneurysm formation by detecting increased levels of nitric oxide synthase protein within the affected blood vessel⁴⁸. These nanorobots can be given the capability to wirelessly communicate information about pertinent vascular changes to care providers, potentially decreasing screening costs of imaging and frequent follow up visits. Importantly, developing the platform required for this device will also enable horizontal expansion of the idea for many other uses, such as tumor detection or ischemic changes.

Oncology

Improving the treatment quality and clinical outcomes of cancer patients, and reducing the mortality and morbidity associated with oncological conditions and their treatment has been identified as a goal by the Institute of Medicine⁴⁹. This need is underscored by the increasing number of seniors in the population, and the increasing number of cancer diagnoses that comes with an aging population. Nanotechnology has already shown much promise in improving the management of cancer. Increasing the sensitivity of cancer imaging tools⁵⁰, overcoming drug resistance⁵¹, and improved treatment of metastasis⁵² are some examples of nanoparticle technology's increasing role. There have also been some promising developments in the subfield of nanorobotics for the treatment of cancer, which will be discussed below.

One of the limitations of conventional chemotherapy has been the toxic effects on normal cells by the chemotherapeutic agents limiting the dose. This limitation has been improved upon as targeted therapies have developed, and as nanoparticle technology has improved the selectivity of treatment⁵³. The development of a nanorobot that can autonomously detect cancerous cells, and release treatment agents at the site of these cancerous cells has been successfully developed⁵⁴. This nanorobot can be constructed to respond to a number of different cell surface receptors, and the payload it releases upon activation can also be changed as necessary. This nanorobot has been constructed using engineered DNA strands that have been made to fold into a desired tertiary structure⁵⁵. Upon binding the desired target, the conformation of the DNA nanorobot undergoes a structural reconfiguration and shifts from a closed to an open state⁵⁴, releasing the stored therapy.

As the above example demonstrates, there is potential in the idea of an autonomous nanorobot circulating through the bloodstream with the ability to selectively release treatment only in the necessary areas. This can be accomplished through a nanorobot built of synthetic elements, in contrast to the biological elements of a DNA nanorobot. Freitas proposes the design of what he terms a pharmacocyte, a nanorobot that also contains a therapeutic payload for the treatment of tumors. This nanorobot would have surface binding sites to bind selected targets, self-sufficient energy generation⁵⁶, and locomotive function to move across tissue walls and cell membranes⁵⁷.

There have also been studies exploring the potential incorporation of nanorobots in tumor resection surgeries, to improve the detection and mapping of tumor margins intraoperatively. A similar approach not utilizing nanorobots has been explored and its efficacy demonstrated. The study demonstrated that using a radioactive colloid injection into the prostate the day prior to tumor resection, and then conducting radioisotope guided sentinel lymph node dissection was more sensitive in detecting early metastasis than open lymph node dissection⁵⁸. The implementation of nanorobots can improve upon this procedure by eliminating the need for the patient to be admitted a day prior to the procedure and eliminating the risk of prostatitis associated with the injection. Nanorobots would be administered intravascularly during the procedure in order to detect tumorous tissue margins and metastatic areas. The nanorobots then conglomerate at sites where tumor tissue is

present, and send an electromagnetic localizing signal to the operating surgeon for mapping⁵⁹.

Nanotechnology has created the opportunity for numerous ways to improve cancer therapy and as nanorobotic technology progresses, it is doubtless that more applications will be envisioned. Further development of the existing technology towards the proposed designs has the potential to establish new standards in the treatment, screening, and prevention of cancer.

Vascular

Though the premise of intravascular therapy for a diverse number of conditions has been described more than a century ago⁶⁰, it has been over the past couple of decades that intravascular therapy has become established as a mainstay of treatment for conditions ranging from aneurysms and tumors to atherosclerosis. The development of nanotechnology has increased the efficacy of existing technologies and is leading the development of new methods for the treatment and prevention of disease through the vascular system⁶¹. We will give a brief overview of some of the emerging applications of nanorobotics towards intravascular therapies.

The use of nanorobots intravascularly greatly expands the potential for screening and monitoring for life-threatening health conditions, as well as monitoring the development and progression of chronic diseases. Examples of life-threatening conditions that could be screened for include brain aneurysms⁶², cancers with no current screening protocols such as lung cancer⁶³, and unstable atherosclerotic lesions⁶⁴. Intravascular nanorobots would constantly circulate and provide current information at any desired moment. Integration with current technology would also allow constant syncing wirelessly, and immediate notifications of changes in health status. The monitoring of chronic health conditions such as diabetes⁶⁵ increases the capability for optimally managing chronic diseases. Improvements in primary prevention capabilities have been the hallmark of improved quality of life and life expectancy in our society, in addition to cost savings⁶⁶. Intravascular nanorobots are potentially the next stage in the continued development of our primary prevention capabilities, and will likely contribute to making our health care system more lean and effective.

In addition to screening and monitoring capabilities, nanorobots can be developed for the application of direct intravascular therapy. For example, in the case of coronary artery stenosis, nanorobots could provide direct therapy to the target area either mechanically or with pharmacologic treatment⁶⁷. Nanorobots also have use in the prevention and acute treatment of aneurysm rupture. The intravascular navigational ability of a nanorobot can allow localized drug delivery to reduce the amount of bleeding, as well as a localization tool as an adjunct to imaging⁶⁸. Additionally, nanorobots can be used for the detection and direct treatment of cancer⁶⁹. The ability of intravascular nanorobots to constantly circulate can provide constant tumor surveillance. For treatment purposes, use of a nanorobot for direct local treatment delivery can improve efficacy by allowing delivery of a higher treatment dose due to a more limited volume of distribution resulting in lower potential toxicity.

Intravascular nanorobotics is a promising area of current development within nanotechnology. The technological capabilities are present for these designs, and as the current proposals undergo development and proof of concept studies, it will be a number of years before nanorobotics enters the clinical environment on a widespread scale. As nanorobots begin to emerge as treatment adjuncts, they will improve efficacy of current treatments and our overall ability to prevent, detect, and treat illness.

Conclusion

The scientific community is in the midst of a breakthrough in developing technology on a scale orders of magnitude smaller than ever before. As our technology advances, and as we explore on smaller and smaller scales, we are able to gain increased control of the world around us and ourselves. In the past, developing the ability to manipulate the world on a smaller scale brought transformative changes to the scientific community, and the world at large. Whether it was the age of microscopes ushering in the area of bacteriology, or the beginning of the atomic age with the study of particle physics, nanotechnology is poised to change many of the paradigms with which we think about disease diagnosis, treatment, prevention, and screening. Outside the bounds of medicine, nanotechnology will affect our lives in countless other ways through industries such as telecommunications and agriculture.

This review provided a brief outline of nanodevices and nanorobotics in medicine, a small subset of the massive field of nanotechnology and nanobiotechnology (see table 1 for a summary of topics discussed). Nanorobotics are developing wide potential applications across all fields of medicine, and expanding the number of therapeutic options available, while also improving the efficacy of existing treatments. It is certainly possible within a generation of time that the use of nanorobotic technology will become ubiquitous in medicine.

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Table I

Overview of the existing and emerging nanorobotic applications across specialties of medicine.

Specialty	Brief Description	Reference
Microbiology	Use of magnetotactic bacteria to transport and navigate nanorobots	12, 13, 15
Hematology	Circulating “respirocyte” nanorobots to deliver oxygen and return remove waste products from periphery	22
Hematology	Circulating “clottocyte” nanorobot with hemostatic functions	26
Hematology	Phagocytic “microbivores” with customizable antigen binding sites for targeting of pathogens	28
Dentistry	Dental anesthesia and sensitive teeth through nanorobot penetrating dentinal tubules for occlusion or administration of targeted analgesic	31, 32, 35, 36
Dentistry	Enhancement of the success rate of root canal procedures by providing visualization of root	33
Dentistry	Improved daily dental hygiene and teeth cosmetics by replacement of enamel layers	32
Neurosurgery	Single axon manipulation and transection with use nanoknife	42, 43
Neurosurgery	Circulating nanorobot for the monitoring of intracranial aneurysm development and progression	48
Oncology	Screening nanorobot circulating and monitoring for detection of neoplasia	54
Oncology	Direct drug delivery to cancerous tissue to limit systemic toxicity and increase effectiveness	57
Oncology	Mapping of margins of tumor to improve resection during surgery	58, 59
Vascular	Screening for atherosclerosis, cancer, aneurysms, and more	62-64
Vascular	Localization of bleeding site for assisting embolization	68