

A proposition of future applications of
Nanotechnology, with specific reference to the
traversing of the blood-brain barrier, for the
delivery of diagnostic and therapeutic agents

By

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PASS WITH MERIT

Research paper based on
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and extended autonomous research

Abstract

The emergence of a more detailed understanding of Nanotechnology in recent years has induced great excitement into many scientists of diverse disciplines, with the potential applications of such engineering looking increasingly promising. Principally, nanotechnology is the exploration and exploitation of matter at a molecular level, to fabricate essentially any structure from 'bottom up'. Current applications of nanotechnology, with principal focus on the medical profession, include the implantation of nanoparticles into antimicrobial bandages, and the specialised embedding of carbon nanotubes as 'scaffolding' in blood vessels.

This paper encompasses the prospect of nanotechnology and its potential incorporation in the field of medicine. The abundance of prospective applications of nanotechnology in life sciences is rising exponentially, and showing considerable promise and clinical relevance in many specialties; including some attention to the field of neurology. One particular application presently considered achievable as a result of pioneering research is the passage of nanoparticles across the blood-brain barrier and into the cerebrospinal fluid. This could allow for the delivery of substances with medical benefit or diagnostic probes to the brain and spinal cord, which are presently unable to traverse the tissue when suspended in the blood vessels of the body.

Towards the latter of this paper, I will also endeavour to highlight just a few of the controversial ethical issues surrounding nanotechnology and its future.

Introduction

In 1959, Richard Feynman, an illustrious physicist and Nobel laureate, encapsulated the idea of atoms obtaining new yet unpredictable properties at an atomic and molecular level, when he presented a speech in which he distinctively said, 'there's plenty of room at the bottom'. This was one of the first proposals in which nanotechnology was regarded as an innovative field of engineering; a great alteration on the previous dubious opinions of scientists who considered it unfeasible by mankind, due to the scale of the science. Shortly subsequent to this change in perspective, the pioneering field developed at a staggering rate and evidently continues to do so.

Nanotechnology - the word 'nano' being derived from the Greek language, meaning 'midget' or 'dwarf' - is a reasonably recent field of science, concerning the study and utilization of matter on a molecular scale, where the properties possessed by the structures appear to considerably differ from those we encounter on a human scale. Such revolutionary properties can include an increase in strength and stability and consequently, improved functionality of the structures, which when accompanied by the weight reduction of nanotechnology, can dramatically enhance materials. For example, nanotubes - folded sheets of hexagonally arranged carbon atoms - amazingly acquire a hundred times the strength of steel, yet simultaneously weigh one sixth the weight of steel. These radical properties exhibit major potential for the use of such nanostructures in diverse fields of research, such as medicine; an area which incessantly

demands technological advancements to enable improved healthcare worldwide. The increasing demand to competently understand how modern medicines work at the molecular level is encouraging a major shift towards predictive, preventive and more personalised health care, which nanotechnology could have the potential to provide. The preferred and more successful realms of medical nanotechnology application and development currently lie in drug delivery systems, cancer diagnosis and the detection of infectious microorganisms. But the scarcity of current operational nanotechnology in medicine could be allowing for avoidable problems which are most definitely undesirable.

Given the inherent nanoscale of receptors, pores and other functional components of living cells, in depth monitoring and examination of these components could be made feasible by the advancements of a new class of nanoscale probes. Nevertheless, nanotechnology is such a recent and unfamiliar extension to modern medicine that many are sceptical of its place in today's society, possibly because of unidentified risks it itself could withhold, and the colossal problems we could face if it were to be abused.

Discussion

At present, medical techniques and the instruments employed to carry them out are crudely invasive with much physical interference, in relation to the prospective, fabricated structures of the nanometer scale. To date, the entry of the skull cavity for medical intervention requires invasive surgery which is frequently accompanied by countless risks. The infliction of damage to cells of the body is an inevitable element of conventional medical procedures, but with nanotechnology convincingly emerging, this could possibly be avoided in the future. The delivery of therapeutic medicines or diagnostic probes to specific areas of the body and more exclusively the brain, with the aid of nanotechnology, looks to be a promising resolution to this possibly unnecessary surgical intrusion. Conversely, the blood-brain barrier presents further issues regarding the delivery of these therapeutic or diagnostic agents solely to the brain with nanotechnology, as a result of the barrier's unique configuration.

The blood-brain barrier mechanism regulates the movement of substances suspended in the blood, into the cerebrospinal fluid (CSF), thus into the spinal cord and ultimately, the brain. The tight seal of endothelial cells, that lines the blood vessels of the brain, selectively permits the passage of only non-ionic and low molecular weight molecules soluble in fat, which include

caffeine and antidepressants. Furthermore, although it may seem a paradox, glucose - a primary source of metabolic energy for neurons and glial cells - is similarly able to traverse the barrier thanks to specialised transporter systems, rooted in the endothelial lining. The complex structure of such a mechanism is crucial to the survival of organisms that possess a brain, because it protects the central nervous system from various circulating toxins and similarly harmful molecules, which are suspended in the blood. On the contrary, it unfortunately also functions as a major impediment to the brain-specific delivery of therapeutic molecules, which are required for the combat against neuronal diseases and disorders, such as brain tumours, neuro-AIDS, drug addiction and obesity.

As a consequence of the selective permeability of the blood-brain barrier, diagnosis or treatment of a brain injury or illness poses a problematical challenge for those in the medical profession, with the prevailing difficulty being the means by which therapeutic agents can be delivered to specialised regions of the brain, crossing this neuroprotective separation. Similarly, in some instances, molecules with therapeutic or diagnostic benefits cannot be purely concentrated to the brain, spinal cord and cerebrospinal fluid by this partially-permeable division, but are able to diffuse around a large proportion of the internal systems of the human body. This is occasionally a result of the inimitable properties of the blood-brain barrier which can allow undesirable traversing of certain molecules. An example of this problem which frequently arises in even modern medicine is the inability to concentrate Thrombolysis infusion to the blood vessels exclusively located in the brain of a patient, who has recently suffered a Cerebrovascular Accident (CVA). The molecules are able to circulate in the lumen of the body's blood vessels and essentially dissolve plaques that line the vessels; a possible cause of such an event. This may appear beneficial to the patient's condition but frequently causes further internal bleeding by the unwanted breakdown of blood clots elsewhere in the body.

A recent outcome of extensive nanoscale research is the creation of a nanoparticle-based platform which discretely enables nanoparticles to traverse the endothelial cell lining of the blood-brain barrier, allowing entry of the nanoparticles into the cerebrospinal fluid (CSF). Certain proteins and peptides, such as the iron-transporting protein Transferrin, efficiently cross the blood-brain barrier when they are required to transport essential nutrients to the brain. These nutrients would otherwise be unsuccessful in trying to reach the blood vessels within the skull cavity

because their properties do not complement the barrier-crossing mechanisms.

One medical proposition which has suffered similar inconveniences in the past is the access of therapeutic or diagnostic nanoparticle-agents. Quantum rods are an example of these innovative agents, highlighted by their versatility to function as diagnostic molecules and as carrier molecules of therapeutic agents. Furthermore, they have a very low toxicity and acquire the ability to be easily incorporated with other molecules, due to their large surface area, which provides optimistic potential for the targeted therapy of disorders of the central nervous system.

Encouragingly, recent studies conducted by the University of Buffalo, indicate that when Transferrin is linked to Quantum rods, types of semiconducting nanocrystals, both molecules were able to successfully transmigrate the partially-permeable blood-brain barrier (clearly shown in Figure 1). This image highlights the abundance of Quantum rods that

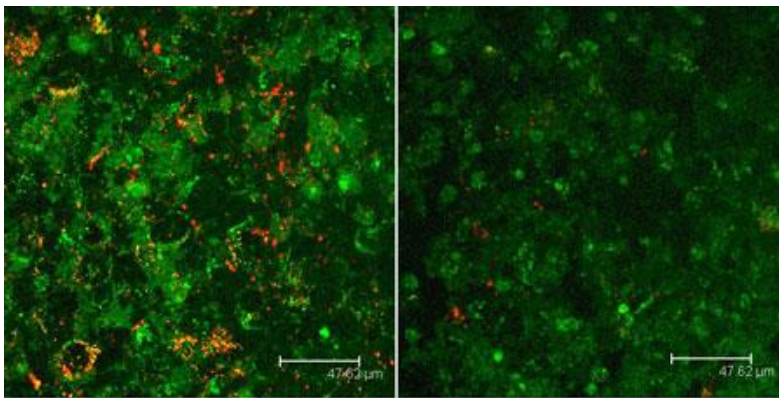


Figure 1. *Microscopic images of Blood-brain barrier model treated with transferrin-conjugated quantum rods (left) and unconjugated quantum rods (right). (Image: Dr. Prasad, the University of Buffalo)*

successfully crossed the blood-brain barrier when linked with the nanocrystals, Transferrin, relative to the absence of the rods when the Transferrin molecules were not linked to them. It also demonstrates the ability of the pioneering technology to produce direct visualisation of the crossing of biomolecules.

In addition, it suggests that this application could facilitate the production of diagnostic nanoprobe for early detection and diagnosis of diverse disorders of the brain. I find this extremely significant in the ongoing development of drug and probe delivery systems because the results suggest that minimally invasive procedures, involving nanoparticles, are sure to be feasible in years to come. This research also implies that we will be able to gain an enhanced understanding of the blood-brain barrier, including an elucidation of the mechanisms that govern its structure, and the efficiency of its operation.

An additional area of research performed over the last few years involved the employment of nanoparticles able to safely cross the blood-brain

barrier, with the objective of illuminating brain tumours in mice when scanned using Magnetic Resonance Imaging (MRI). These diagnostic nanoparticles were fabricated with groups of molecules injected with infrared dye, and advantageously obtained the selective ability to cross the blood-brain barrier without inflicting any damage to it.

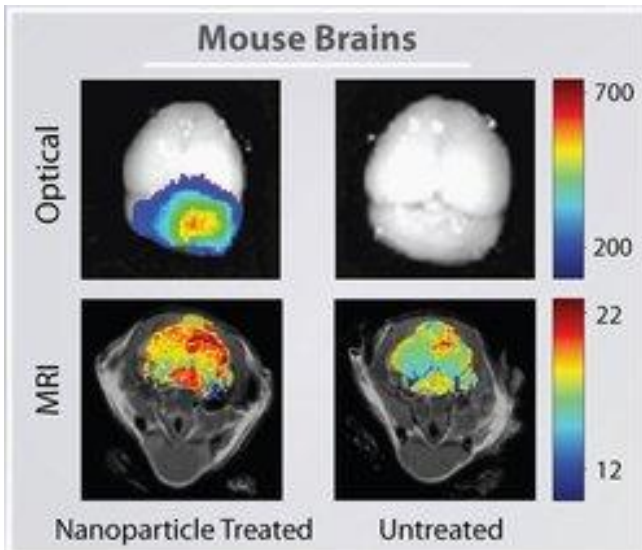


Figure 2. 'Brain Tumour Painting', the illumination of brain tumours in mice with the help of infrared nanoparticles injected into the bloodstream.

Subsequently, it was injected into the bloodstream of each mouse, and when the mice were scanned, the contrast of the images produced drastically improved, in relation to conventional scanning techniques, clearly highlighted in Figure 2.

Originally, the research was conducted for the analysis of brain cancer which unfortunately remains one of the deadliest cancers, and typically one of the hardest to successfully treat. However, I am certain that this research will stimulate the further exploration of such dynamic molecules, which currently I can

only see as beneficial.

Conclusion

Nanotechnology looks to be an integral part of future medical practicing, but due to our present limited understanding of the field, we are most certainly still uncertain of the issues it could present on application. Overall, based on the research pivotal to this paper, I believe that nanotechnology will be fundamental in delivering both therapeutic and diagnostic agents to the brain, traversing the blood-brain barrier effectively, efficiently but, predominantly, by a safe means. Transferrin will certainly play an essential role in the transport of agents such as Quantum rods across the almost impermeable barrier, as it has shown desirable actions which will considerably enhance the science. Similarly, dye-injected nanoparticles present qualities which could have a positive effect on the development of nanotechnology.

One issue that needs to be addressed in the near future, is the liberal movement of nanoparticles due to their size. Initially, this appears to be an advantage of the atomic-scale technology; however, the lack of sufficient control of these unpredictable molecules gives rise to concerns that some nanoparticles could be toxic. Scientists are anxious that certain nanoparticles, destined for specific areas of the body other than the brain, could inadvertently cross the blood-brain barrier, causing adverse affects on such a vitally protected organ. I do sincerely consider this to be a precarious element of the technology, however I am convinced that the progression of nanotechnology will only occur if safe practice is employed, hopefully avoiding any major problems which would alter its path of progression.

Personally, nanotechnology appears to be an innovative science that has interminable potential if research is conducted effectively. The secure crossing of the blood-brain barrier by medically beneficial molecules is a fundamental example of potentially successful applications, and following extensive research, I am sure that the technology will be applied to human healthcare, in the near future. Consequently, I envisage nanotechnology to provide healthcare on a level which no other technology currently presents. In my opinion, nanotechnology is promisingly demonstrating the ability to provide innovative advancements to medicine and as a result, I believe the outcome will be entirely personalised healthcare.

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