

Nanotechnology in the Treatment of Brain Tumours:
Potential innovations and applications

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Abstract

As brain tumours present specific challenges in terms of treatment, alternative and more effective possibilities are under relentless research. Nanotechnology provides a plethora of opportunities to improve and expand on such treatments, and throughout this paper we shall postulate as to the possible further uses of nanotechnology in the treatment of brain tumours. Specifically, we will predict additional ways in which two current treatments under development could be improved and enhanced, via the inclusion of nanoparticles, in order to treat brain tumours; incorporating a selection of our own ideas regarding nanotechnological application. The potential flaws in these treatments include: the possible destruction of healthy brain tissue, a heightened vulnerability of the brain's inner systems, and difficulties involving pre-existing metallic implants in the body- which could prevent treatment due to magnetic properties.

Introduction

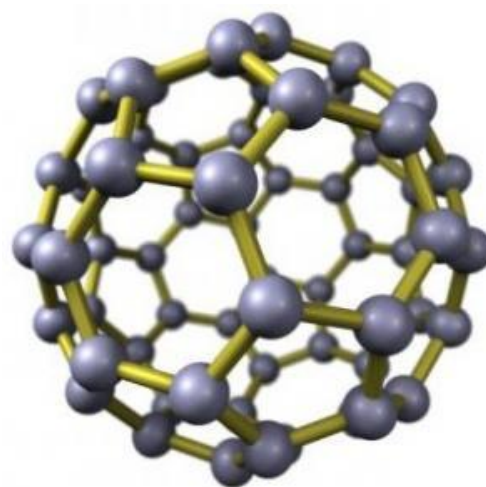
Nanotechnology is generally defined as the study and manipulation of substances at a molecular and atomic level- that is, the scale of its eponymous measurement, the nanometre, or 10^{-9} metres. Furthermore, nanotechnology is conventionally defined as being in the dimensional range of 1-100 nanometres, as stated by the National Nanotechnology Initiative (NNI).¹ The term 'nano-technology' itself was first used and defined by Norio Taniguchi in 1974 as the 'processing of separation, consolidation, and deformation of materials by one atom or one molecule'.² However, the first conceptual ideas of nanotechnology were described by Nobel Laureate physicist Richard Feynman, at the annual meeting of the American Physical Society in 1959 at the California Institute of Technology, in his lecture 'There's Plenty of Room at the Bottom'.³ This talk is said to have kick-started, and given basis for, the future development of nanotechnology.

Such ideas were further developed, as molecular nanotechnology, focusing on molecular assembly, by engineer K. Eric Drexler at the Massachusetts Institute of Technology (MIT) during the late 1970s. Drexler's ideas were fully realised in his 1986 book, 'Engines of Creation: The Coming Era of Nanotechnology',⁴ considered the first book on the subject. In this he considers and imagines the economic implications of nanotechnology, the possibilities of its medicinal application, and its impact on the environment.

However, one invention, five years before the 'Engines of Creation' was released, was absolutely fundamental in precipitating the further advancements in nanotechnology throughout the 1980s, and indeed, up to the present day- the Scanning Tunnelling Microscope (STM). This device allows the user to 'see' at the nanoscale; rendering any manipulation and handling at this level more plausible than ever before.⁵ This creation in turn facilitated the discovery of buckminsterfullerene⁶ in 1985- carbon's third allotrope, consisting of twenty interconnecting hexagons and twelve pentagons (together comprising the C_{60} molecule, a representation of which is shown in figure 1). 'Buckyballs', as they are colloquially known, have a particularly vast array of possible applications- ranging from lubricants to drug delivery systems, and as such are the subject of major research and exploration. The

Figure 1

*A molecule of
buckminsterfullerene; C_{60} .*



development of such research resulted in the discovery of carbon nanotubes in 1991⁷, which possess both remarkable strength and conductivity- both thermal and electrical.

But what are nanotechnology's contributions to medicine? 'Nanomedicine' as a field presents a myriad of ground-breaking treatments, both current and conceivable for the future, which will invariably and irrevocably change the face of medicine. The inner workings and mechanisms of all the cells, enzymes, and proteins of the body are at the nanoscale; nanotechnology's inherent purpose to influence and rework systems at this level will allow the maximum possible fine-tuning of treatments- potentially rendering surgery unnecessary. In particular, there has been substantial progress made in the area of drug delivery systems- here nanoparticles' size compared to the various components of a cell becomes especially relevant; these cellular components will inevitably be the target sites of particular drugs used in treatment, and an appropriately small delivery system will allow for more precise distribution of the drug in question, as well as ensured penetration of the cell membrane in order to achieve this. In addition, nanoparticles are the only colloids⁸ that can be administered intravenously without accumulating in the blood.⁹ However, crucially, nanoparticles, specifically nanocapsules or nanospheres, entirely surround a drug, wholly protecting it from chemical and biological attack until it reaches its destination; this also helps prevent any harmful side effects the drug may have, as the drug is put to use only at the desired site, and is otherwise protected from causing any additional harm. These particles can be further engineered so as to be biodegradable, allowing them to be broken down in the body after use.¹⁰

Drug delivery systems utilising nanotechnology-explicit accuracy and stability, in that they do not react with the species they encapsulate, have been the subject of a large amount of research in the field of oncology. For example, radon can be caged by C₆₀ molecules coated in tumour- targeting antibodies. The cancer cells proceed to adsorb the molecules, and the radon emits α -rays, which destroy the cancerous cells, whilst leaving other tissues of the body unaffected due to the- rays' short range.¹¹ In addition to such treatments, gold coated silica-core nanoshells, of approximately 120nm in diameter, have been used to destroy tumours in mice at Rice University, Texas.¹² Again, by conjugating specific antibodies or peptides to the nanoshells' surface, as in the radon treatment with C₆₀ molecules, the nanoshells can be made to target cancerous cells. The tumour is then irradiated with an infrared laser- this heats the gold to such a degree that it causes the cancerous cells to die.¹³

Nanotechnology-related characteristics of heightened precision and exceptional success in tumour treatment have inevitably been applied to the healing of brain tumours. The most recent advancements in this area of study include work by German research team Charité, involving the introduction of iron oxide nanoparticles, treated by an alternating magnetic field, into cancerous cells. This treatment similarly involves the generation of heat to destroy directly or weaken the cells, only via the oscillations of the nanoparticles as a result of the high frequency magnetic field.¹⁴ Ultimately, we have found that the treatment of brain tumours is perhaps nanotechnology's most relevant field of treatment due to this organs delicacy and the difficulties surrounding alternative drug treatments, owing to the protective properties of the Blood- brain barrier.¹⁵

Discussion- by Thomas Merewether

Amongst the treatments with the most scope for nanotechnological application, further application, in this case, is a therapy created by American inventor John Kanzius, known as Kanzius RF Therapy. This treatment involves the exploitation of an exceptionally valuable property of radio waves: they pass through human tissues without causing any ill effect, yet heat any metal they happen to come across on their way. The therapy specifically involves the introduction of colloidal gold nanoparticles- where the particles of gold are usually suspended in water- or Single-Walled Carbon Nanotubes (SWCNTs) into the tumour site, whereby radio waves are used to excite the nanoparticles- producing heat and ‘cooking’ the aggregation of tumour cells, destroying them.¹⁶ During research, only liver cancer cells were tested with the therapy. However, with modifications, the therapy could be used to treat brain tumours. Firstly, the Blood-brain barrier must be overcome, as the nanoparticles are administered systemically, as a minimally invasive treatment; without temporarily disabling the defensive nature of the Blood-brain barrier, the supplying of these drugs to the brain would be, although perhaps possible owing to the small size of the particles and the piercing needle-like properties of SWCNTs, far more difficult and certainly more time consuming than otherwise. To achieve this, a technique pioneered by Edward Neuwelt of Oregon Health and Science University can be used, involving the administration of a concentrated sugar solution via a catheter inserted into the femoral artery, which is then led up to one of the arteries near the base of the brain. The solution is hyperosmotic: that is, it has a higher solute concentration than the surrounding endothelial cells. Consequently, water is drawn out of the endothelial cells that comprise the Blood-brain barrier, causing them to shrink, and thus widening the tight junctions between the cells and allowing substances to diffuse from the bloodstream into the brain.¹⁷ Secondly, the nanoparticles must be treated so that they can target the tumour cells- so enough particles physically aggregate at the tumour site to result in its destruction, and so that the eventual heat energy produced is concentrated only at the site of the tumour, and not anywhere else in the brain. This can be accomplished by covering SWCNTs with monoclonal antibodies- antibodies of the same type which can be made to target specific cancerous cells. In addition, SWCNTs can be covered in folic acid as a way of giving them targeting properties; cancerous cells have a large number of folic acid receptors integrated into their plasma membranes, meaning they have a very high affinity for these molecules. This ensures the SWCNTs accumulation at the tumour site.¹⁸

Ultimately, these alterations to standard Kanzius RF therapy would make it a practical and effective treatment of brain tumours. However, one particular innovation, set to completely revolutionise modern medicine, would further increase the efficiency of this therapy: the advent of the ‘nanorobot’.¹⁹ A single remotely-controlled nanorobot, constructed principally out of carbon (either diamond or fullerene, or a mixture of both), with the correct nanofacilities constructed (intrinsic sensors, nanocomputer, etc.), could be made to have both the requisite concentrated sugar solution for penetration of the Blood-brain barrier, and the SWCNTs themselves for the therapy, internalised; ready for distribution when and where necessary. After the nanorobot had entered the brain, and dropped off its SWCNT contents, it could then leave the brain and enter the bloodstream, where it is then capable of being removed from the body via a catheter or similar mechanism.

Furthermore, as well as being used to enhance treatments themselves, nanorobots could be used effectively in the diagnosis of tumours. As the technique for Blood-brain barrier perforation utilises osmotic imbalance only, it can be, theoretically, performed repeatedly without any damage to the cells of the barrier- they simply swell back up to normal size again

after the osmotic imbalance is restored. Moreover, nanorobots can have monoclonal antibodies bonded to them to target cancerous cells in much the same way SWCNTs can. Using these features, nanorobotic ‘check-ups’ could be introduced at regular intervals for high risk patients, such as: those with a family history of brain tumours, those exposed to ionising radiation or certain chemicals in their daily life²⁰, or symptomatic patients. These individuals could have a nanorobot ‘search’ their brain via monoclonal antibodies for any cancerous cells. Such a technique would ensure correct and early-as-possible diagnosis, and so would remove the need for any other diagnostic techniques. Such early diagnosis would be a particularly important innovation, as symptoms for brain tumours are often very similar to other diseases, and by the time a tumour is diagnosed and subsequent treatment has ensued the tumour has often caused significant damage to the individual, including possible cognitive and behavioural problems, visual impairment, and facial paralysis.²¹

Discussion- by Rebecca Man

The research I will be focusing on is the application of photosensitizers as a treatment for brain tumours using nanotechnology. Photosensitizers work to treat cancers via the following mechanism²²:

1. The photosensitizer is administered to the patient.
2. The photosensitizer is exposed to light of a particular wavelength (normally in the visible spectrum).
3. The photosensitizer electrons are excited from the ground singlet state to the excited singlet state.
4. Inter-system crossing occurs, where the promoted electron spins the opposite way. This results in the triplet excited state being achieved.
5. Upon having achieved the triplet excited state, the photosensitizer contains molecular oxygen.
6. The photosensitizer and the molecular oxygen are proximate, which results in an energy transfer, whereby the photosensitizer relaxes back to the ground state.
7. A singlet excited oxygen molecule is created (as a result of the previous step).
8. This singlet oxygen molecule is very aggressive and destroys nearby molecules, hence killing cells.

Firstly, the photosensitizer would need to be administered intravenously; this presents the problem of how to overcome the Blood-brain barrier.²³ Problems also arise when considering how to deliver light of the right wavelength to the brain. Delivery using endoscopy or a catheter, as with other cancers, such as skin cancer, would not be possible; penetration of the skull would be necessary in such methods, and the risk of damage to the brain would be too great.

However, nanotechnological techniques could be utilised in order to help deliver visible light to the brain. Currently, a material known as a phosphor can change absorbed energy in tissues into visible light without being heated to high temperatures.^{24, 25} Using nanoparticles, with their properties of longer life-span and improved efficiency, which comes as a result of increased surface area to volume ratio, a ‘nanophosphor’ could be created and then delivered to tissues. In comparison to a bulk phosphor, less light would be re-absorbed from the visible light generated, and therefore more could be used in the activation of the photosensitizer.²⁶

Additional problems may occur in the distribution of the photosensitizers, due to delivery to cells having to be highly selective. Also, although previously the photosensitizer has been delivered intravenously, photosensitizers are not readily soluble in water-based substances (blood in this case) and so other substances must be added, which may be toxic if present in sufficient amount.²⁷

These issues may be overcome via the use of silicon-based nanoparticles. The inclusion of silicon in the nanoparticle would increase water-solubility, and mean the molecule could be permeated by smaller molecules such as singlet oxygen- which is needed to activate the photosensitizer.²⁸ This would mean the nanoparticle would not have to physically release its contents to tumour cells, removing the need for a further substance to facilitate this release.

Moreover, silicon’s inclusion would mean other beneficial characteristics of the element could be harnessed. The unique ability of silicon to incorporate magnetite nanoparticles (three molecules of iron and four of oxygen) would mean delivery of the photosensitizer to cells could be controlled by an exterior magnetic force. With only the silicon nanoparticle and its contents being affected by this field, no other cells would be damaged and normal brain function would remain maximal.

Likewise, silicon in the encapsulating nanoparticles could result in the beneficial breaching of the Blood-brain barrier. Although protecting the brain from many substances within the blood that would disrupt the brain’s delicate microenvironment, the barrier does allow through certain nutrients which the brain requires in order to function. This includes low-density-lipoproteins, which bind to specific receptors on the brain's surface at the interface with the bloodstream. These are then transported into the brain by receptor-mediated endocytosis.²⁹ Therefore, it would seem that if these lipoproteins could be effectively incorporated into the silica just as magnetite nanoparticles were, then the nanoparticle and its contents could reach the brain.

Not only would a technique such as this minimize harm to the brain, but it may also be a more sustainable and cost effective approach to treating brain cancer. Simple intravenous nanoparticle administration, perhaps via the common carotid artery, would mean a surgical procedure would not be necessary. Usage of a magnetic field to control which cells were exposed to the photosensitizer would further decrease the need for numerous stages of treatment with requisite specialized and expensive equipment. Together these factors could eliminate waiting time for treatments, making them more readily available.

Conclusion

In conclusion, the suggested techniques for overcoming brain tumours using nanotechnology are as follows:

- The use of SWCNTs, which can be excited using radio waves in order to produce heat, thus destroying cancerous cells. Covering the nanotubes in monoclonal antibodies would ensure delivery only to specific cells and prevent damage to other areas of the brain.
- The usage of nanorobots to both diagnose and treat brain cancer. Delivery and consequent removal of the robot could take place via the bloodstream, using a catheter or similar mechanism.
- The usage of photosensitizers and activation via a nanophosphor. As a result of the nanophosphor having a larger surface area to volume ratio in comparison to a larger phosphor, less visible light would be re-absorbed and the photosensitizer would be activated more efficiently.
- Increasing the specificity of the area targeted by incorporation of silicon into the nanophosphor. This would mean magnetite particles could be incorporated and movement throughout the brain could be controlled using an exterior magnet.

Inevitably, there are several prospective problems with the treatments suggested in the discussion. The potential destruction of healthy brain tissue surrounding the area to be treated, in both treatments covered, is a concern. Firstly, Kanzius RF therapy works by excitation of particles via radio waves, specifically metals or SWCNTs, resulting in the release of heat to destroy tissues. Therefore, it would follow that any metal present in the head of the patient- for example, reparative plates for a skull fracture- could also be heated as well as the desired nanotubes, causing potential injury to surrounding tissue. This problem could be addressed by concentrating the radio waves very specifically, so that only the tumour site itself is exposed to the waves- perhaps even involving emission of the waves at the nanoscale to ensure only the SWCNTs involved in the therapy receive them.

Secondly, the proposed phosphor in the following treatment, needed in order to supply light of the right wavelength to the photosensitizer, works via changing the energy it absorbs into visible light. The phosphor would not, however, absorb all the energy provided as a means of producing visible light; some leftover waste energy is unavoidable, and this may be concentrated in the surrounding tissues, perhaps damaging healthy brain tissue. Again, solving this issue would involve markedly concentrating the energy supplied to the nanophosphor, so no energy becomes concentrated at all in surrounding tissues- again, possibly involving energy emission at the nanoscale in order to achieve this level of specificity.

Additionally, another problem is that, in the time during which the Blood-brain barrier is disabled as a necessary requisite for the Kanzius RF therapy, and the nanoparticles pass from the bloodstream into the brain, other substances from the bloodstream could pass into the brain and disrupt the chemical and electrical signals necessary for correct neuron signalling. Under these circumstances, even a common bacterial infection could take hold of the brain while it is exposed.³⁰ This problem could be tackled by ensuring that the osmotic imbalance

fundamental in the ‘opening’ of the barrier only exists for the minimum amount of time needed, meaning the barrier remains dysfunctional only long enough for the SWCNTs to cross it.

Moreover, in the treatment involving photosensitizers, the magnetic field used to control the direction of the silicon nanoparticle during its delivery to the tumour could critically affect any metal-based medical implants- in the head, but also, depending on the intensity of the magnetic field used, all across the body. In this way, a large number of very common therapies could become contraindications for this treatment, including pacemakers and coronary stents. Unfortunately, patients with such devices would most likely be prevented from undergoing this treatment- unless the particular material used as an implant was one impervious to the effects of a magnetic field, such as Titanium and its alloys. Furthermore, future research into fullerene-based medical implants, having a significant advantage over metal ones in terms of increased strength as well as lightness, could mean carbon-based implants will replace metal ones in the coming years- resulting in no magnetism-related complications, and therefore, manageable treatment.

Finally, another inescapable result of research of this category is the incurrence of a certain amount of ethical controversy. For example, bestowing SWCNTs with targeting properties may involve the use of monoclonal antibodies, the production of which involves the deliberate, if unavoidable, generation of cancer in mice.³¹ This degree of suffering in animals will be seen as totally unacceptable by many parties, so must be addressed. A possible solution to a subjective problem of this variety is to adhere to current animal welfare guidelines; accompanied by continually striving to reduce animal suffering in the production of monoclonal antibodies to the absolute minimum. Perpetual assessment of the necessity of animal suffering should also be carried out: to ensure that any pain is kept to a minimum, and so that, within reason, any animal suffering can be substituted for similar circumstances involving human volunteers.

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