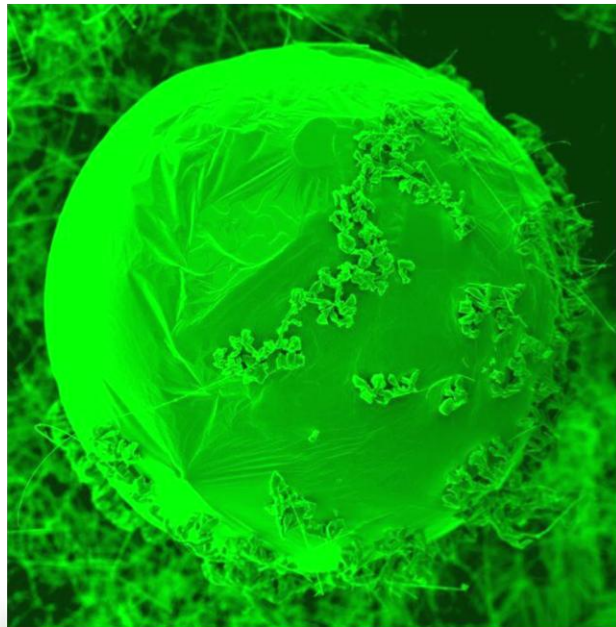


**USES OF NANOTECHNOLOGY IN DETECTION AND TREATMENT  
OF CANCER**

**BY**

**GEORGINA NDUKWE**

**PASS WITH DISTINCTION**



**RESEARCH PAPER  
BASED ON  
PATHOLOGY LECTURES  
AT MEDLINK 2010**

## ABSTRACT

Nanotechnology is one of the most exciting and fastest developing concepts of modern sciences. Nanotechnology has the potential to exhibit essential implications in methods of detection and treatment in medicine. Cancer is a frightening disease and is estimated to affect up to one in three people at some stage in their life. However, there may be justification and means for an alternative. I would like to propose the use of polymer-based nanostructures in the transport of chemotherapeutic drugs. In addition, this paper proposes that the incorporation of this treatment with nanoparticle magnets may be a favourable way of combatting subsequent recurrences of cancer that so often result in death.

## INTRODUCTION

In around 1985, observations were made that indicated the presence of new types of carbon chains in red giant stars. As they attempted to recreate these chains in the laboratory, they unwittingly created one of the most exciting nanoscale structures in science today: the fullerene (a football-shaped cage of carbon atoms). In 1991, carbon nanotubes were also discovered, hence the birth of a whole new chapter in science: nanotechnology. In 1978, Rohrer and Binnig developed the electron microscope which meant that later these entities could be perceived and managed at a nanoscale level.

Nanotechnology allows you to solve immense problems with minute tools. Nanotechnology literally means “technology at a miniscule scale” and can be used in medicine, computing, the environment and various other fields. Nanotechnology truly has the potential to transform so many aspects of our daily lives<sup>[18]</sup>.

Nanotechnology is of huge relevance to a number of the problems still faced in medicine today. Nanoparticles are useful in the pharmaceutical industry, predominantly due to their minute size, which results in much larger surface areas. Nanoparticles of substances possess the ability to penetrate cell membranes when the equivalent as larger particles of the exact same substance cannot<sup>[12]</sup>. Buckminsterfullerenes in particular have the ability to prevent incarcerated atoms from being adversely affected by cells of the body. This concept has led to the delivery of drugs which otherwise would be susceptible to attack from enzymes found within organisms. This means that they can be protected whilst being transported to their target sites. Developments in nanotechnology thus far have already led to earlier detection of traditional diseases which provoke an immune response. Quantum dots bind to antibodies when they are produced and fluoresce when the antibodies fasten to pathogens, allowing infections to be detected and located<sup>[1]</sup>. Nanotechnology has also allowed for several diagnostic tests to be incorporated into a very small space, for example onto a chip. This allows these tests to be conducted much faster than sending samples to a laboratory, which saves valuable time in the process of diagnosis. There are many possible uses for nanotechnology in medicine, but arguably the most exciting prospect in nanomedicine today is their capability to revolutionise the manner in which we diagnose and treat cancer<sup>[19]</sup>.

When devising new applications for nanostructures we must consider the practicality of introducing such nanostructures into organisms in the least invasive manner possible. This means we must consider the ability of the chosen nanoparticles to overcome various obstacles in the body such as the blood-brain barrier<sup>[2]</sup>. It is also advisable to thoroughly ensure the particle is biocompatible and not cytotoxic before incorporating it into a medical procedure. It ought to be noted that materials in the nanoscale have significantly different properties to their larger scale counterparts and clusters or aggregations of nanoparticles have dissimilar properties to both of these.<sup>[5]</sup> These points can be considered as ethical considerations to do with safety rather than drawbacks of nanomedicine. The benefits of using nanostructures in medicine far outweigh the scientific effort required to surpass the obstacles in their developments. Most of these benefits are due to their very small size in relation to other structures such as, cells, viruses and proteins that exist in the body. There is a lot of diversity in the types of nanoparticles available for medical applications. One example is the fullerene, which has been investigated for its potential as a vehicle for

drug-delivery<sup>[3]</sup>. In addition, there are various polymer-based nanostructures which have many benefits when incorporated into drug-delivery systems. Another important consideration when attempting to incorporate nanotechnology into diagnostic and therapeutic tools for cancer is to ensure that developments are not just for development's sake and there is a real benefit compared to the current method. This paper will explore how nanotechnology can improve the diagnosis and treatment of cancer.

## DISCUSSION

### Diagnosis of Cancer

Currently, the diagnosis of cancer is a many staged process involving imaging tests (such as X-rays, CT scans, MRI scans, ultrasound scans and positron emission tomography scans), genomic tests (such as BRCA 1 and 2) and biopsies. These tests are not always conclusive; for example an abnormal mammogram does not always necessarily presage that a patient has cancer. In addition, the danger of exposing tissue to X-ray radiation must also not be overlooked. Genomic tests do not cover the entire range of genes which can result in the formations of cancers (*i.e.* oncogenes) and thus can result in a false sense of security which can cause a patient to be less likely to undergo regular testing. Biopsies are invasive and by the time a tumour is obvious enough for a biopsy to be taken it may be too late and a patient's chance of survival may have significantly depleted<sup>[21]</sup>. As detecting cancers in their pre-malignant stages improves the prognosis significantly, early detection of cancer can be the difference between long life and early death. It is thus evident that early diagnosis of cancer is the best way to improve the survival rate following cancer treatment.

Although the levels of efficiency and competence of current imaging techniques are constantly being enhanced, there is a considerable difference between their current sensitivities and those required to detect the indiscernible agglomerations of early stage cancerous cells. Polymer-based nanoparticles can be used in the detection of cancer because of their capacity to be purposefully manipulated. This will enable them to target specific cancerous cells and release contrast agents only when they reach these cancerous cells. This possibility arises as a result of incorporating different functional groups or moieties onto the "polymer matrix" which then bind to specific cancerous cells<sup>[2]</sup>. The nanoparticles can be conjugated with more than one functional group or moiety; therefore they can be designed to adhere to more than one type of cancerous cell. This could allow for more than one aspect of cancer being tested for simultaneously. The release of contrast agents, as previously mentioned, can be made to occur in a more controlled manner than those in more traditional imaging techniques. These agents can be dissociated from the nanoparticles as the nanoparticles themselves degenerate. The rate of disintegration and thus the rate of contrast agent dissociation depends upon the "polymer matrix". The rates can be orchestrated to depend upon the immediate environment of the nanoparticles, including factors such as pH and temperature<sup>[2]</sup>. They can thus be designed in such a manner that they recognise the conditions of a tumour. L. E. Gerweck observed that extracellular pH of tumours is significantly lower than the extracellular pH of normal cells and, as a response, degrade releasing the contrast agents into the cancerous tissue.<sup>[4]</sup>

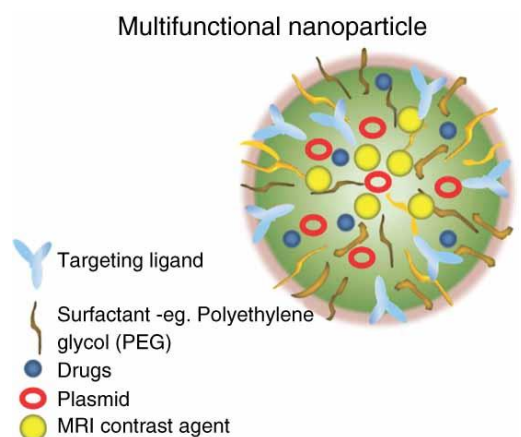


Figure 1 shows a multifunctional nanoparticle<sup>[22]</sup>

The use of iron oxide nanoparticles as a contrast agent in magnetic resonance imaging could improve several forms of cancer detection for various reasons<sup>[16]</sup>. It would be less invasive than a biopsy and also pose less risk of resulting in another tumour forming than an X-ray. It could be developed in such a manner that it provides conclusive, more

accurate diagnoses than MRI scans currently and, most importantly, it could increase sensitivity of MRI scans, allowing cancerous cells to be detected at a much earlier stage as well as in much smaller numbers, before tumours even begin to become conspicuous. These nanoparticles may become advantageous over other alternatives due to their dual applicability in detecting and treating cancer. Also, if one wanted to incorporate detection and treatment into one procedure, you would need to ensure, beyond reasonable doubt, that the detected cells were cancerous. This would be a stage at which magnetic nanoparticles which could “scan” DNA for the presence or absence of known oncogenes could be of great use<sup>[14]</sup>. Otherwise, you could run the risk of killing non-cancerous cells unnecessarily.

Another consideration is the biocompatibility or cytotoxicity of potential nanoparticles. It is evident that experimental confirmation must be acquired but it has been suggested that the use of nanoparticles to transport contrast agents in fact increases biocompatibility as the contrasting agents are prevented from reacting with any aspect of the biological environment. In addition, their ability to access all possible areas of the body where tumours can arise could be an additional advantage. The nanoparticles can easily have a coating layer into which polyethylene glycol can be incorporated, allowing nanoparticles to survive in blood plasma for an increased length of time. The surface coating can also contain polysorbate (which is a surfactant) thus improving the nanoparticles propensity to traverse physiological obstructions such as the blood-brain barrier. This attribute could be crucial in early detection brain tumours.

A question that has thus far been left partly unaddressed is why a nanoparticle polymer matrix is required as opposed to simply inserting contrast agents directly into the body in their “free” state. As previously indicated, releasing unconstrained imaging agents into the body can result in reactions between naturally occurring biological molecules and the agents. Because enzymes are unable to enter the nanoparticle, these reactions can be prevented. If fluorescent imaging agents are used, which are a valid alternative to the use of iron oxide nanoparticles, photobleaching is a frequent complication which can easily be reduced by encasing the fluorescent imaging agents within the nanoparticles, as the diffusion of oxygen is reduced<sup>[2]</sup>. The nanoparticles allow targeting of cancerous cells due to association of various specific moieties, meaning that the image contrast agent molecules are focussed in areas where they are needed.

## **Treatment of Cancer**

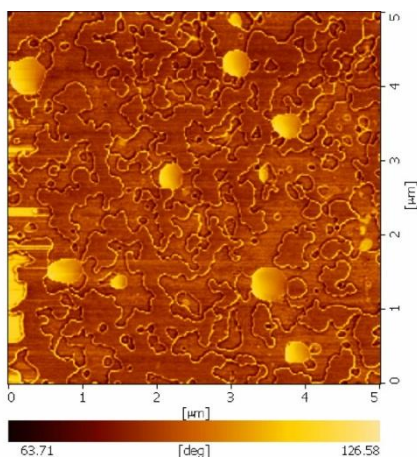
Once an accurate and conclusive diagnosis has been made, a patient undergoes one of the most exhausting and uncomfortable treatments in medicine today. Often the treatment for cancer may incorporate one or more of the following aspects: radiotherapy, chemotherapy, surgery and photodynamic therapy. Photodynamic therapy is one of the newer forms of cancer therapy which is based on nanotechnology.

There are numerous drawbacks of the traditional methods of cancer therapy which scientists and medical professionals have been working to alleviate for several years. Radiotherapy is largely associated with great levels of side-effects and morbidity. There are concerns for patients undergoing radiotherapy as it comes with an increased risk of malignant tumours developing in the vicinity of the original tumour as a direct result of the irradiation.

Chemotherapy is effective in destroying cancerous tissue, as the drugs work by disrupting some part of the cell cycle. Some inhibit DNA replication during interphase: others interfere in the metaphase period of mitosis by impeding spindle formation. The main flaw, and the factor that often contributes to cancer treatment having a reputation as a therapy laden with side effects, is the fact that chemotherapeutic drugs are not selective as to which cells they affect and therefore can damage normal cells. They are just as effective at killing rapidly dividing cancerous cells as rapidly dividing healthy cells. One of the most well-known side-effects of chemotherapy is hair loss. The reason behind hair loss during chemotherapy is the nature of hair follicles. Their rapidly dividing cells are strongly affected by chemotherapeutic drugs, which are designed to target cells which multiply the fastest. Other cells which are affected

by chemotherapeutic drugs are cells lining the mouth. We all know mouth cells are easily removed, a factor which is an advantage for things like swab tests. This would indicate that these cells are often and easily replaced. Cancer patients are unable to replace mouth cells which are constantly being “brushed off” causing frequent mouth sores which can be extremely uncomfortable for a patient. Also, cells in the digestive system such as stomach and bowel epithelial cells are constantly being “brushed off” by the flow of material through the digestive system. Normally, the cells lining the digestive tract replace themselves roughly every few days. In patients undergoing chemotherapy, these rapidly dividing cells are targeted and killed resulting in a great deal of pain and other additional symptoms such as diarrhoea. Blood cells only last in the body for approximately 100 days, which suggests that blood cells are constantly produced by rapidly dividing cells. This can be suppressed by chemotherapy resulting in a low blood count. Another drawback of chemotherapy is the balancing act that must be performed in order to ensure that enough of the chemotherapeutic drug has been given to kill the cancerous cells as effectively as possible, but keep the side-effects as low as possible. Since the advent of chemotherapy, doctors have had to just accept the fact that to lengthen their patients’ lives they would have to inflict temporary suffering upon them. This makes the search for a treatment which is just as effective, if not more so, but with significantly fewer side-effects a very important one. Nanotechnology can help tremendously in this regard. There are ways that nanoparticles can be incorporated into chemotherapy, radiotherapy, photo-dynamic therapy and thermotherapy.

Polymer nanoparticles may be used as drug carriers in nanomedical chemotherapy. For example, O.C. Farokhzad *et al.* used biodegradable copolymer nanoparticles to target prostate cancer cells. Experiments both *in vivo* and *in vitro* verified that utilising targeted nanoparticles<sup>[7]</sup> as transport agents in chemotherapy appreciably improved the survival of mice who had undergone a xenograft<sup>[10]</sup> (a graft of transplanted tissue containing the prostate specific antigen<sup>[11]</sup>) to 100% (after 109 days) compared to 57% survival using non-targeted nanoparticles and only 14% using the chemotherapeutic drug alone<sup>[2]</sup>.

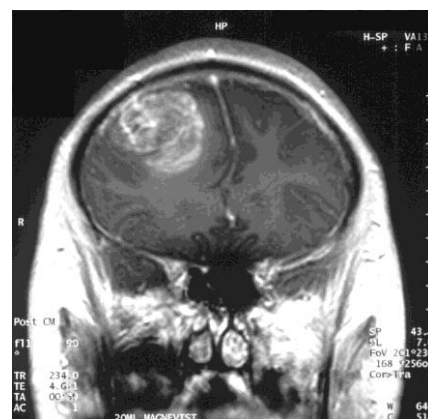


**Figure 2: Solid-lipid nanoparticles observed by AFM<sup>[24]</sup>**

Solid lipid nanoparticles are useful for the treatment of brain tumours<sup>[6]</sup>. This is attributable to their ability to traverse the blood-brain barrier. It is believed that endothelial cells may absorb the solid lipid nanoparticles by engulfing them<sup>[8]</sup>. This is thought to be made possible by the adsorption of plasma proteins onto the exterior of the solid lipid nanoparticles. The lipid matrix entraps the drugs, shielding them from the internal biological environment. The exterior coating of solid lipid nanoparticles can also dictate the discharging of drugs into the cancerous tissue at which they were targeted. However, further research is required to combat the fact that the drugs that have been

successfully transported by these particular nanoparticles, namely paclitaxel and Dox are substrates of p-glycoproteins which are used by the body in a protective mechanism or a “drug-efflux system”. Further investigations are needed into what would be an appropriate drug to use in partnership with solid lipid nanoparticles, which would allow them to be used to their potential, without limiting effectiveness.

Glioblastoma multiforme is an extremely aggressive type of brain tumour which affects the glial cells<sup>[9]</sup>. These cancer cells often overexpress receptors for low-density lipoproteins because they have a greater demand for lipids, since their rapid multiplication makes for a high metabolic rate. This fact could be used in the development of a new drug-delivery mechanism that imitates low-density lipoproteins. S.C. Steinger has shown that you can load poly(butyl cyanoacrylate) nanoparticles with drugs and coat them with polysorbate, which then imitate low-density lipoproteins and at the blood-brain barrier, endocytosis transports



**Figure 3: MRI scan showing glioblastoma**

the nanoparticles inside the brain as if they were low-density lipoproteins<sup>[2]</sup>. This comes with risks due to nanoparticles entering the brain which could have unforeseen side-effects. Therefore more research would be needed to address these ethical issues.

Dr Andreas Jordan has been developing a new method of treating brain tumours using superparamagnetic iron oxide nanoparticles to destroy cancer cells using heat<sup>[23]</sup>. A controlled amount of heat is produced using a low frequency magnetic field, created by an electromagnet or a “nano-activator”, which causes the nanoparticles to turn thousands of times per second, thus creating heat. The side-effects are low and it harnesses the fact that there is a natural barrier around the tumour due to the constitution of normal tissue being very different to that of tumour tissue. These nanoparticles are easily monitored using MRI, allowing this procedure to be a safer, more effective method of treating brain tumours.

Firstly, combining this form of treatment with certain imaging methods could be a logical development, creating a simultaneous detection-treatment system. This principle would use the fact that iron oxide nanoparticles are effective as both imaging and therapeutic agents. The iron oxide nanoparticles would be initially inserted into polymer-based nanostructures *in vitro* before being inserted into the body. These nanostructures would first have to undergo chemical adaptation when they would be conjugated with several cancer targeting moieties. It is important that many of these moieties are naturally-occurring within the patient and not man-made, so as to prevent their rejection. This obviates the need for immunosuppression to avoid the possibility of rejection. The migration of the agents to the tumour site may be monitored by MRI and when a tumour has been detected the treatment phase may then begin. By applying a magnetic field in the manner previously described, heat can be generated from the inside of the tumour, thereby killing the cancerous cells or making them more susceptible to chemotherapy.

Another development could be to combine this treatment with a modified form of chemotherapy, to create a vigorous treatment with fewer side-effects. This could be achieved by a method similar to that just described. You could in the same vehicle include chemotherapeutic agent-containing nanostructures as well as iron oxide-containing nanostructures. These could be modified to only break down and release the chemotherapeutic agents when in the precise heat generated by the superparamagnetic iron oxide nanoparticles. This would make the tumour more susceptible to the chemotherapy. This would also cause the chemotherapy to be more precisely targeted to cancerous cells alone. Also, these nanomagnets can remain, packaged in the body, with no ill effects, as a special tissue gradually builds up around them. So you could use them repeatedly in patients, simply by exposing them to a low frequency magnetic field again and again. This may help combat the problem of recurrent tumours in patients.

## **CONCLUSION**

Nanotechnology is an emerging technology that has great potential in medicine. It has tremendous potential in the diagnosis and treatment of cancer. Nanotechnology gives us the opportunity to develop new and more effective ways for early diagnosis in cancer. It can also enable us to develop more effective treatment in cancer by more precise targeting of cancer cells. However, there are safety issues which must be addressed before this innovative treatment could be introduced into clinical practice. This treatment could form the basis for future development and investigation into the potential of nanotechnology to contribute to a wide range of treatments high therapeutic indexes and low side-effects. This could improve the efficacy and safety of cancer treatment in the future.

## REFERENCES

### **Book-based references:**

- [1] Altavilla, C., Ciliberto, E. (2011) *Inorganic Nanoparticles*, Taylor and Francis Group, LLC
- [2] Broz, P. (2010) *Polymer-Based Nanostructures: Medical Applications*, The Royal Society of Chemistry
- [3] Langa, F., Nierengarten, J. F. (2008) *Fullerenes: Principles and Applications*, The Royal Society of Chemistry

### **Journal-based references:**

- [4] Gerweck, L. E., et. al. (2006) Tumor pH controls the *in vivo* efficacy of weak acid and base chemotherapeutics. In the *Journal of Molecular Cancer Therapeutics*, 5, 1275–9
- [5] De Jong, W., Borm, P. (2008) Drug delivery and nanoparticles: Applications and hazards. In the *International Journal of Nanomedicine*, 3(2), 133-149

### **Web-based references:**

- [6] Drug Delivery: fatty problem  
<http://asia.iop.org/cws/article/news/43947>
- [7] Cell surface receptors  
[http://en.wikipedia.org/wiki/Cell\\_surface\\_receptor](http://en.wikipedia.org/wiki/Cell_surface_receptor)
- [8] Endocytosis  
<http://en.wikipedia.org/wiki/Endocytosis>
- [9] Glioblastoma multiforme  
[http://en.wikipedia.org/wiki/Glioblastoma\\_multiforme](http://en.wikipedia.org/wiki/Glioblastoma_multiforme)
- [10] LNCaP  
<http://en.wikipedia.org/wiki/LNCaP>
- [11] Prostate specific membrane antigen  
[http://en.wikipedia.org/wiki/Prostate\\_specific\\_membrane\\_antigen](http://en.wikipedia.org/wiki/Prostate_specific_membrane_antigen)
- [12] The A to Z of Nanotechnology  
<http://www.azonano.com/Details.asp?ArticleID=1699>
- [13] BBC – Health: Cancer  
[http://www.bbc.co.uk/health/physical\\_health/conditions/in\\_depth/cancer/index.shtml](http://www.bbc.co.uk/health/physical_health/conditions/in_depth/cancer/index.shtml)
- [14] CancerQuest Section Summary: Oncogenes  
<http://www.cancerquest.org/oncogenes-summary>
- [15] Research Interests of Jun Zhang  
<http://www.cs.uky.edu/~jzhang/Research.html>

- [16] Science Daily: Iron Oxide Nanoparticles Becoming Tools for Brain Tumor Imaging and Treatment  
<http://www.sciencedaily.com/releases/2010/08/100802165455.htm>
- [17] Nanostructures in Biodiagnosis  
<http://www.tinhoahoc.com/Nanotechnology/Nanodetector1.pdf>
- [18] What is nanotechnology? From Micro to Nano and new Applications – Institute of nanotechnology  
<http://www.nano.org.uk/what-is-nanotechnology>
- [19] What is nanotechnology? Nanotechnologies for Medical Applications – Institute of nanotechnology  
<http://www.nano.org.uk/nano/whatisNEW2.htm>
- [20] What is Nanotechnology? Nanomaterials, Nanoparticles, Carbon Nanotubes – Institute of Nanotechnology  
<http://www.nano.org.uk/nano/whatisNEW3.htm>
- [21] The differing effects of biomaterials in the human body – News – Institute of nanotechnology  
<http://www.nano.org.uk/news/1195/>
- [22] Taming “hotspots” with new method – News – Institute of Nanotechnology  
<http://www.nano.org.uk/news/1202/>
- [23] Localized heating using gold nanoparticles – News – Institute of Nanotechnology  
<http://www.nano.org.uk/news/1192/>
- [24] Nanoparticles lessen side effects of potent cancer drug – News – Institute of Nanotechnology  
<http://www.nano.org.uk/news/1169/>
- [25] Tiny Trojan horses deliver a cancer drug to cell nuclei – News – Institute of Nanotechnology  
<http://www.nano.org.uk/news/1164/>

**Image references:**

- [26] Title page image  
<http://library.thinkquest.org/07aug/02147/particlegeneral.html>
- [27] Figure 1  
<http://media.wiley.com/wires/WNAN/WNAN125/mfig002.jpg>
- [28] Figure 2  
<http://images.iop.org/objects/asia/news/1/10/2/liquid1.jpg>
- [29] Figure 3  
[http://upload.wikimedia.org/wikipedia/commons/thumb/c/cb/Glioblastoma\\_-\\_MR\\_coronal\\_with\\_contrast.jpg/617px-Glioblastoma\\_-\\_MR\\_coronal\\_with\\_contrast.jpg](http://upload.wikimedia.org/wikipedia/commons/thumb/c/cb/Glioblastoma_-_MR_coronal_with_contrast.jpg/617px-Glioblastoma_-_MR_coronal_with_contrast.jpg)