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The Pathology Project – Nanotechnology Applications  
Cancer Therapy

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Research Paper  
Based on  
Pathology Lectures  
At Medisix 2011 and current literature

### Abstract

Nanotechnology research and development has provided many field, medicine in particular, with many opportunities. There are over 200 different types of cancer, and in 2008 309,527 people were diagnosed in the UK, in the same year 156,000 people died as a result of cancer. Over the last 30 years cancer mortality has fallen by 20%, and as progression in this field of research continues, the aim is to keep decreasing the mortality rate. ([http://info.cancerresearchuk.org/prod\\_consump/groups/cr\\_common/@nre/@sta/documents/generalcontent/018070.pdf](http://info.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@sta/documents/generalcontent/018070.pdf)) There are many possible avenues to explore with regards to cancer diagnosis and treatment, and Nanotechnology research in this area is proving exciting, through its current successes in research to its further possibilities. This paper discusses current research and the potential for future work on Nanotechnology in Cancer therapy.

### Introduction

Nanotechnology involves the use of objects smaller than 500 nanometers (nm) in size (typically between 0.1nm and 100nm), this means working at the scale of atoms. The properties of structures at this scale are unique, and are not seen in molecular or macroscopic structures. Nanotechnology includes the use of Carbon Nanotubes, Quantum Dots, Nanowires and Iron Oxide Nanocrystals, to name a few. It can be argued that Nanotechnology was born in 1959 after a speech was delivered at the annual meeting of the American Physical Society by Richard Feynman. In this speech he talked about 'a field in which little has been done, but in which an enormous amount can be done in principle', and 'manipulating and controlling things on a small scale' (<http://www.zyvex.com/nanotech/feynman.html>). Experimenting in the field of Nanotechnology truly began in the 1980's by scientists in Switzerland. These scientists from IBM built the first Scanning Tunnelling Microscope (STM) in 1981. The STM enables the viewing of surfaces at an atomic level and its creators were honoured with the Nobel Prize in 1986. The STM allows good resolution at 0.1nm and enables its user to view and manipulate singular atoms; this is possible for atoms in a variety of mediums including many liquids or gases and within a large temperature range.

A Carbon Nanotube is made up of rolled up sheets of Carbon Hexagons, and were discovered in 1991. Carbon Nanotubes belong to the same structural family (fullerene) as 'Buckyballs', also known as Buckminsterfullerene. Buckminsterfullerene is the most common in terms of its occurrence in nature. 'Buckyballs' were discovered in 1985. The diameter of a Carbon Nanotube is just a few nanometers, approximately 10,000 times thinner than a human hair, yet can be quite long. Carbon Nanotubes come under two categories, single walled Nanotubes and multi walled Nanotubes. A single walled carbon Nanotube consists of a single shell, and a multi walled carbon Nanotube has several shells.

Quantum Dots are nanoparticles constructed from semiconductor materials, they range from 2 to 10nm in diameter. Again, their size provides them with unique properties, such as optical properties, which has encouraged research into their use in Solar Panels, LEDs and medical imaging. (<http://www.newscientist.com/article/dn9939-instant-expert-nanotechnology.html>).

### Discussion:

Nanotechnology and its advances and potential uses have implications for many different areas, a key field being medicine. The uses of nanotechnology in the field of medicine are potentially endless, from delivery of medications to disease

detection, the progression of nanotechnology research could change healthcare outcomes for millions of people.

Single Walled Nanotubes have been studied for their potential uses in cancer treatment. A study in California showed cancerous cells within a tumour could be selectively damaged and destroyed using this type of Nanotubes. The single walled Nanotubes were carefully introduced into tumours, into the cancer cells, and then near infrared radiation was used which triggered cell death only to the cells containing the Nanotubes (Samson C 2005). It has been shown that a solution of Nanotubes would heat up to 70 degrees Celsius in a few minutes during exposure to an near infrared light. After the Nanotubes are introduced to the tumour and exposed to near infra red light it is the heat produced which damages the cells. This could be used in conjunction with the nanotechnology used to identify the cancerous cells which would assist this treatments effectiveness, all of the cancerous cells could be identified and then treated with the single walled Nanotube and infrared radiation method, yet leave healthy cells unharmed.

The diagnosis and treatment of Cancer could both benefit from nanotechnology involvement. A study focussing on the diagnostic involvement of nanotechnology in Breast Cancer has provided some interesting possibilities into the identification of cancerous tumours. Profiling of tumour biomarkers can be used in diagnosis, this profile can be obtained from single tumour sections by conjugating nanoparticles to antibodies. (Cuenca, A 2006). Through this method it has been predicted that at least ten more cancer associated proteins can be detected and identified using small sections of tumour, currently three cancer proteins have been identified as associated with breast cancer. The ultimate goal of this technique is to use nanoparticles to target tumours; research into drug delivery through nanotechnology has also been explored. This method of essentially 'bar coding' key parts of the DNA can be applied to many conditions involving DNA alternations, and could be used for many medical diagnoses. This could potentially be used as a genetic screen, to systematically identify key alterations in the DNA structure associated with various conditions, then the biomarking technique would be used to identify which alterations have occurred in an individual, perhaps pre-empt a conditions at its asymptomatic phase and treat pro-actively instead of reactively, with cancer in particular an early diagnosis plays a vital role in the outcome. Perhaps more excitingly Supermagnetic Nanoparticles have uses as contrast agents for the detection of cancer in vivo; this could be used to monitor the response to various treatments and tumour progression. Medicine is moving fast towards personalised care and away from 'one size fits all' therapy, unique treatment plans based on individual needs, and this research is leading towards personalised oncology which may improve the outcome for the patient.

Another method of diagnosis has been identified through nanotechnology – Nanowires. (<http://www.newscientist.com/article/dn9939-instant-expert-nanotechnology.html>). The method involves coating Nanowires with DNA sequences which correspond with disease causing bacteria or viruses, and if the Nanowire is introduced to this pathogen DNA in a sample it will bind to it, this process alters the conductivity of the Nanowire. The presence on the pathogen can then be noted after simply spotting a change in the conductivity of the Nanowire, which can be detected by attaching each Nanowire to a microchip transistor. Working at the 'nano' scale allows detection within very small samples. Each Nanowire is approximately 700nm wide and 8 micrometers long. The microchip used has microwells in the centre and electrodes on either side which create an electricity gradient; this gradient is then used

to coordinate the Nanowires into position. Once the Nanowires are coated in DNA, they are drawn across the microchip electric field until they reach a microwell, they are then fixed into place. For detection of different viruses or bacteria, the DNA which coats the Nanowires is changed to the appropriate DNA for detection using this method. (<http://www.newscientist.com/article/dn16434-nanotech-gadget-could-diagnose-any-disease.html>). This method is still under development as there are some issues with the positioning of the Nanowires within the microchip microwells, working at such a small scale has made this manoeuvring difficult. This method could be used in the future for early detection of viruses and bacterial infections, and would be particularly useful where early diagnosis and fast treatment is crucial for a successful outcome. Using this method of protein detection could be potentially applied to genetically caused conditions, for example, it could be used in pre-natal genetic screens. There are many ethical issues surrounding pre-natal screening, should the results show that the unborn child will be born with downs' syndrome for example, this information may then be passed to the mother so that she can make an informed decision about whether to continue with the pregnancy or to terminate it, the decision may be based on the parents perceived notions of the child's quality of life, which potentially devalues the lives of adults with physical disabilities, suggesting that they are not valued members of the community, however this is only one side of the argument. The very purpose of these types of screen is to provide options, to be able to choose what happens next, pre-natal screens in particular, some conditions may require very expensive 24 hour care, such as Retts Syndrome, this could be a significant financial drain on a family and the parents may be unable to provide this kind of care, in this case a choice to terminate the pregnancy may be in the best interests of the family as a whole.

Screening for viruses and bacteria may also be useful as a pro-active treatment for cancer, using the example of Cervical Cancer. The Human Papilloma Virus (HPV) can increase a woman's risk of developing cervical cancer. Most women that acquire HPV do not go on to develop cervical cancer, however approximately 70% of cervical cancers are caused by various types of HPV. HPV can lead to genital warts as well as changes in the cervix or vagina which can lead to cancer. A vaccine has recently been brought out to national distribution to young girls of about 13 years old, this prevents them from at least 70% of cervical cancer causes, theoretically, and so women over the age of 13 have not received this vaccine and are still at risk. The ability to identify viruses in small sample could be applied here, although there is no effective treatment against HPV, its early detection would identify a woman at risk of changes in the cervix or vagina and could then have regular screens, any identified changes are spotted early and may pre-empt the development of cancer by removal of the altered tissue. (<http://www.cancerhelp.org.uk/about-cancer/cancer-questions/cervical-cancer-vaccine>).

One of the potential uses of Nanotechnology is for progression in the treatment of cancer. A use of nanotechnology for progression in the field of medicine is drug delivery.

Current therapies for cancer are flawed for many reasons, one of which being the unspecific nature of the 'anti-drugs'. At present, chemotherapeutic drugs affect the desired cancer cells and also the healthy cells in the body. The action of the chemotherapeutic drug on healthy cells causes many of the undesired side effects associated with cancer treatment. Ideally the 'anti-cancer' drugs would be administered as an inactive drug, and be somehow only activated once at the desired

location, in this example within the cancerous tumour. This would involve knowledge of the environment within a tumour, identifying how it differs from the rest of the body, and using these differences to activate the 'anti-cancer' drugs, therefore having no effect on the other cells of the body. This ideal may be becoming reality, with the aid of nanotechnology. The drug of choice is now to be entrapped within a nanoparticle; this may be a physical entrapment or a chemical one. The interaction of the core of the nanoparticle and the drug molecule allow it to be trapped inside, and can now be transported within the nanoparticle vessel. The drug is now administered into the body within a nanoparticle, which prevents its action within the body, leaving it inactive. (Lee, P. 2011).

The bonds formed between the core of the nanoparticle and the drug molecule are crucially important, if the link formed is too stable the delivery of the drug will be delayed and reduce the benefits of this method, and if the link formed to unstable they drug will be released before it reaches its target, again this reduces its benefits as the main issue with current chemotherapy is its lack of specificity. One of the ways that specificity has been addressed is with the use of pH-sensitive linkers, so in an environment such as blood with a pH of 7 the links remain stable, however when entering a tumour which typically has a low pH of around 5 the links destabilise and release the drug, this demonstrates a way of preventing the action of the anti-cancer drugs on the healthy cells in the body and targets the tumour. Another link used may be Disulphide bonds. These are particularly interesting because they can be cleaved by Glutathione by serving as an electron donor. Glutathione presents at higher concentrations within cells than at an extracellular level, this means that when travelling in the blood the drugs remain trapped within the nanoparticle, but once delivered into cells the drug is released. This method involves the use of Polymeric Nanoparticles.

Nanoparticles that are used in drug delivery of cancer treatments may be made from various materials such as polymers, dendrimers, liposomes, viruses, carbon Nanotubes and metals. Polymers selected for use in nanoparticle preparation must meet a set of requirement before they are considered for use, these include biocompatibility, biodegradability and their properties must allow functionalising. Generally the polymers used fall under one of two categories, natural or synthetic polymers. The structure of the polymeric nanoparticles is key for their use in drug entrapment and drug delivery. Polymeric nanoparticles have a hydrophobic core and a hydrophilic shell, this stabilises the nanoparticle in aqueous environments.

Nanoparticles formed from Liposomes have had a few disadvantages, but the main issue with their use appears to have been addressed. The structure of Liposome membranes consist of phospholipid bilayers, the fluid mosaic model of hydrophobic heads and hydrophobic tails gives it the properties desirable for nanoparticle formation. The main problem with using Liposomal nanoparticles was the time that they could be used for, the blood circulation time is very short, and if often cleared out of the blood by macrophages, this is obviously problematic because the drug is unlikely to have reached its target before the immune system acts to remove it. In order to increase the circulation time for these nanoparticles they were coated in polymer, this now allows a circulation time of several days. This does suggest that using exclusively Polymer derived nanoparticles may be a quicker method of nanoparticle production as they do not require a cover of another substance in order to be of any use in drug delivery.

Another advantage of using nanotechnology for the delivery of chemotherapeutic drugs instead of conventional methods is that it offers the potential

to overcome drug resistance, as nanoparticles can bypass the P-glycoprotein efflux pump. A major issue with current cancer treatment is that the cells can become resistant to the chemotherapeutic drugs. The P-glycoprotein is over expressed on the cell surface of tumours and is a cause of multiple drug resistance. Over expression of the P-glycoprotein pump in tumours is linked with a poor prognosis due to the poor response to chemotherapy. There has been research into developing inhibitors to this pump to allow continuous use of the anti-cancer drugs without the build up of multi drug resistance, the inhibitors did show that some drug sensitivity could be restored to the cancer cells however the studies were generally unsuccessful. Nanoparticles can enter cells through endocytosis, therefore avoiding the P-glycoprotein pump altogether. This method of drug delivery should allow the drug to enter the cells and continue to act on the tumour without becoming resistant and studies investigating this have so far produced exciting results. (<http://www.newscientist.com/article/dn9939-instant-expert-nanotechnology.html>).

#### Conclusion:

To conclude, current research is showing that Nanotechnology is an area that could significantly benefit medicine as a whole, and in particular Cancer Diagnosis and Treatment. The benefits of Nanotechnology to drug delivery in cancer chemotherapeutics are exciting, there is the potential to treat tumours and destroy cancerous cells yet cause minimal, if any, damage to the healthy cells surrounding it. The ultimate goal in cancer treatment has always been to treat the cancer without the collateral damage to the surrounding area, and this may now be possible. Administering a drug which is not activated until it enters the tumour may now be possible, this is an incredible step forward and has implications wide outside of cancer, but to medicine as a whole. Research has delivered cancer treatment to a stage where accurate tumour identification, drug delivery, targeted drug action and accurate monitoring of treatment progression is not too far from reality, and further work into this area could lead to personalised oncology, this is vital as no two tumours will be identical, individual differences must be recognised.

Drug resistance is a problem with the treatments of many conditions as well as cancer, so the same principles used to bypass the P-glycoprotein pump would still apply, the nanoparticle used would simply contain the relevant drug and would enter the cell via endocytosis and avoid the build up of a resistance. This working in conjunction with the Nanowire method of detecting and identifying bacteria and viruses in very small samples could potentially eliminate some diseases as they are detected so early on that treatment can begin immediately. Obviously this is a far off goal in the progression of nanotechnology but surely it can be seen how many incredible possibilities there are just in medicine alone. Through various methods and a considerable amount of research it is becoming possible to tackle the major issues of cancer treatment, the ability to target the cancer cells after specific identification is a huge step forward, and work into other areas will only bring us closer to a lower mortality rate for cancer sufferers in the future.

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