

Future Applications of Nanotechnology in the
Detection of Lung Cancer.

BY

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PASS

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ABSTRACT

This paper explores the possible applications of the revolutionary field of Nanotechnology, within the diagnosis of Lung Cancer, which is the most common cause of a cancer death in the UK, Cancer Research UK (2005), which is mainly due to late detection. In this paper I investigate the current research into diagnosing Lung Cancer, using nanotechnology, as well as thinking about what nanotechnology could mean for cancer in the future, whilst examining the ethical issues and physical limitations, of these ideas. Also, looking at the problems with current diagnostics therefore being able to identify which areas nanotechnology needs to build upon.

INTRODUCTION

Nanotechnology, is the study of manipulating matter on a molecular scale, specifically one to one hundred nanometres, with its name being coined by Taniguchi (1974), from the greek word nano meaning 'midget'. This scale is miniscule, a nanometre in comparison to a metre, is the equivalent of a marble to the size of the earth, which provides a huge scope for its development particularly in areas such as Medicine, as it would be able to penetrate a cell membrane.

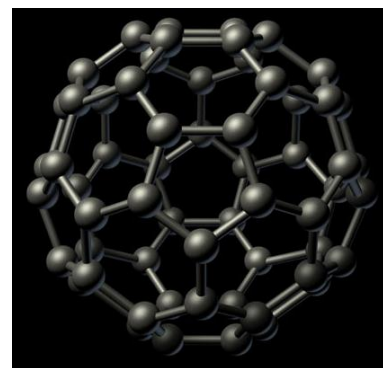
The concept is to copy nature, by building from the 'bottom up', instead of trying to shrink larger machines which has been done by scientists for many years. This concept is often traced back to Feynman's talk entitled 'there's plenty of room at the bottom' (1959), that inspired Drexler to write the Engines of Creation (1986), which outlined the basics of what is now known as molecular nanotechnology. He proposed the idea of a nanoscale 'assembler' which could make items of a basic complexity, as well as copying itself. However, he also brought about the concept of the 'grey goo', when Nanotechnology goes wrong penultimately leading to the hypothetical end of the world scenario.

The invention of the scanning tunnelling microscope, by Binnig and Rohrer (1981), revolutionised nanotechnology, as now scientists could see matter at the atomic level, for the very first time, which allowed them to manipulate matter on the nanoscale, with Binnig and Rohrer famously moving individual atoms to spell IBM (Figure 1), their employer.



Figure 1

Buckminsterfullerene (C_{60}) was prepared by Kroto, Heath, O'Brien, Curl and Smalley (1985), by using laser vaporisation on a graphite target, thus confirming that large carbon clusters were being formed. Buckminsterfullerene currently plays a huge role in Nanotechnology, as it has unique chemical and physical properties, which its allotropes do not. As a molecule it is resistant to shock and extreme temperatures, it can react with vast number of elements as well as free radicals thus helping to complete the polymerisation process, both of these properties



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Figure 2 - Diagram of a Buckminsterfullerene molecule.

are potentially extremely useful in industry. Due to its shape (see Figure 2), it can hold other elements or nanodevices inside, thus being ideal for transportation in Medicine. Especially when potassium or caesium are inserted into its cavity it becomes the best organic superconductor known to man, which indicates that when other elements are inserted into the cavity it may take on other properties.

Although Carbon Nanotubes discovery is generally attributed to Sumio Iijima (1991), however Rudushkevich and Lukyanovich published images of 50 nanometre carbon tubes in 1952, however Iijima did generate exceptional interest in nanotubes and nanotechnology as a whole. These small tubes are from the fullerene family, and are hollow tubes, with their walls being made up of graphene, sheets of carbon one atom thick. Carbon Nanotubes are the strongest materials yet to be discovered, with over one hundred times the tensile stress of steel, making it highly desired by institutes such as NASA. This size and durability makes them ideal for the building blocks for nanodevices, therefore we need to be able to manipulate them. IBM have developed a way of changing the nanotube's position, shape and orientation as well as cutting them, using an atomic force microscope, ergo we can use them like any other building material. In addition to this they can easily penetrate cell membranes, due to their needle like shape, thus they can act similarly to buckminsterfullerene to transport drugs to cells. This could be done by using the 'trojan horse' method, which tricks the cell into accepting the drug by being coated in folic acid.

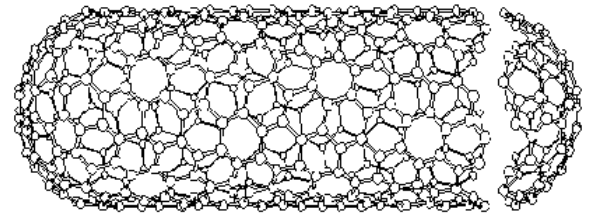


Figure 3 - structure of a carbon nanotube capped with a hemisphere of buckminsterfullerene.

The miniscule scale of Nanotechnology makes it ideal; for uses in Medicine, as a nanodevice should be able to pass through the cell membrane, without the immune system detecting it, therefore it should be able to destroy, or alter, mutated cells. This concept means its scope within oncology is vast, with Industry Today (2011) projecting that 'the anti-cancers segment will dominate the nanomedicine market', therefore in this paper I will mainly be focusing on Nanotechnology's role within Oncology.

Cancer is a group of disorders, caused by cells multiplying uncontrollably, thus often invading other tissues. There are more than 100 different types of cancer, therefore there are six main subcategories; Carcinoma, Sarcoma, Leukaemia, Lymphoma, Myeloma and Central Nervous System Cancers. Most cancers are often triggered by carcinogens, such as the Human Papilloma Virus, or faulty genes, which damage

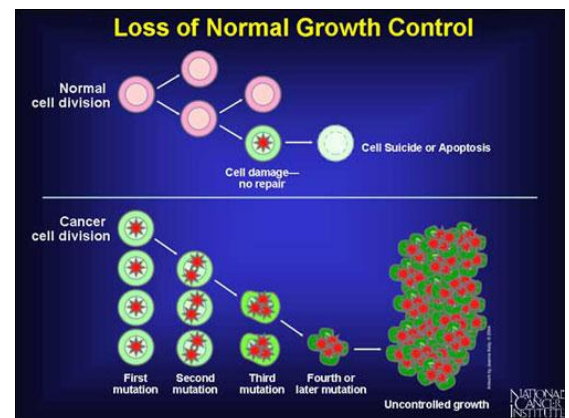


Figure 4-The growth of a tumour

oncogenes, that regulate mitosis, growth, repair and the ability to self destruct. These mutated cells may form a tumour, sometimes it is benign and can easily be removed as they can't spread. However unfortunately sometimes they are malignant, and can invade nearby tissue and spread through the lymphatic system, which are cancerous.

There are already exciting developments, in anti-cancer nanotechnology. Cancer Research UK scientists have developed a treatment, which packages anti-cancer genes in minute particles which targeted tumours in mice, 'once inside the cell the gene enclosed in the particle recognises the cancerous environment and switches on.'. The genes enclosed in the nanoparticles then force the cell to produce proteins that can kill the cancerous cells, thus meaning only cancerous cells are affected. Hopefully, this will have reached clinical trials in a couple of years and will revolutionise the treatment of cancer, as it should vastly improve the survival rates for those with inoperable tumours, and reduce the abhorrent side effects. In addition to this, scientists from six different institutions have created a carbon nanotube that can detect and destroy an aggressive form of breast cancer. It does this by using an avian anti-HER2 antibody, thus reacting strongly with the HER2 protein in the tumour cells while ignoring normal cells. Thus resulting in almost 100% eradication of the cancer cells, however it is still in its very early stages of development.

DISCUSSION

Over 38,000 people are diagnosed in the UK with Lung Cancer, every year making it the second most common cancer in the UK (Macmillan 2010), and the most common cancer worldwide. Unfortunately, it is often diagnosed very late meaning it has a very low survival rate.

The Lungs are a vital organ, which control our breathing, and try to ensure as much oxygen is passed into the circulatory system as possible as well as ventilating the alveoli, which are responsible for oxygen diffusing into the bloodstream. Tobacco is a carcinogenic, therefore almost 90% of lung cancer sufferers are smokers. It's common symptoms being a persistent cough, however is often dismissed as a 'smokers cough', with haemoptysis (coughing up blood), dyspnoea (difficult breathing), and chest pain.

Types of lung cancer

There are three main types of lung cancer:

- **Small Cell Lung Cancer**

This form is usually caused by smoking, however exposure to asbestos or radon is also a factor, it is usually fast growing and spreads quite quickly, within this there are two subcategories; small cell carcinoma (oat cell cancer) and combined small cell carcinoma. Unfortunately at the moment for most patients diagnosed with small cell lung cancer the prognosis is dim, as surgery is very rarely possible, however their prognosis is also based on the stage of the cancer, the patient's gender and the level of lactate dehydrogenase in their bloodstream.

- **Non-small cell Lung Cancer**
There are three main types of non-small cell lung cancer; squamous cell carcinoma, adenocarcinoma, large cell carcinoma. There are many risk factors for non-small cell lung cancer, including smoking, being previously treated with radiation therapy in the chest area, being exposed to asbestos, radon, chromium, nickel, arsenic, soot or tar and living where there is high amounts of air pollution. Generally, the prognosis is fairly good with it often being possible to remove the tumour with surgery in stages 1, 2 and 3, only in stage 4 is the prognosis very poor with chemotherapy to reduce the symptoms being the most popular option.
- **Pleural Mesothelioma**
This is when a tumour forms in the pleura, and is split into three sub categories; epithelial, sarcomatoid and biphasic. Most people who develop pleural mesothelioma have lived or worked in an environment where they inhaled or swallowed asbestos, however being exposed to particular viruses and living with someone who works with asbestos, are also risk factors. Currently there is no cure for mesothelioma unless it can be removed in surgery, however normally it has already spread too far upon detection.

Current Detection and Treatment

Currently the initial form of detection is an X-Ray, which checks for any abnormalities in the lungs, however this is very basic and only gives a rough representation of what could be wrong. However as shown in figure 5, they are very vague images thus leading to many false positive results, National Cancer Institute (2005), therefore a more reliable, cheap method is needed to diagnose lung cancer.

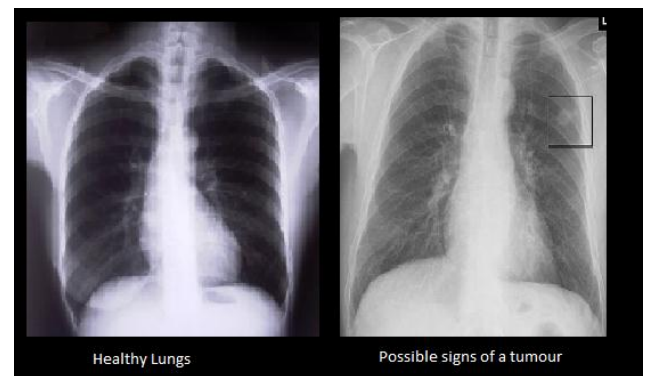


Figure 5

After the initial X-ray, patients are referred to a specialist, who may want to do further tests. This includes an MRI scan, Mediastinoscopy, Thoracoscopy, Lung Biopsy, Endobronchial Ultrasound scan, Isotope Bone scan and lung function tests. Most of these are expensive and invasive however offer much more accurate images than an x-ray, (as shown in figure 6).

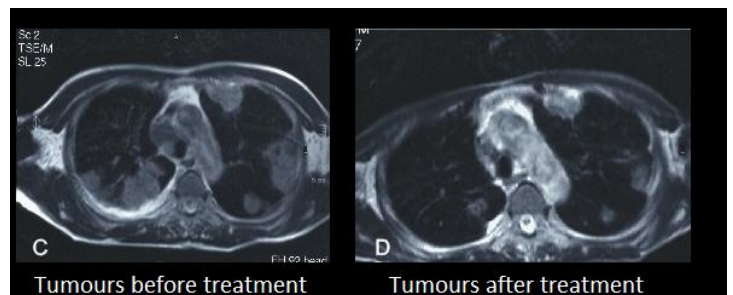


Figure 6- MRI scan of chest

Currently treatment for non-small cell lung cancer, is effectively simple. Stage 1 a lobectomy, pneumonectomy or occasionally a segmentectomy, is performed however if the tumour is too close to the heart, trachea, oesophagus, or a major blood vessel surgery can be very risky. Also, due to most sufferers being heavy smokers other conditions such as emphysema or heart disease, may make surgery too hazardous. In addition to this it takes many weeks to recover

fully from a lung operation, and mild pain can last for several weeks. Also, severe pain can develop sometime after the operation due to the nerve endings growing back.

Another main method of treatment is chemotherapy, which is administered intravenously, and occasionally orally. It works by preventing the cancerous cells from multiplying, assists the immune system and initiates the growth of essential enzymes, despite being classed as one of the most effective measures in treating cancer patients, it had truly horrendous side effects. These side effects include neutropenia (lowered resistance to infection), anaemia, bruising, nausea, hair loss, fatigue and a sore mouth.

The other main method of cancer treatment is radiotherapy, which uses high energy x-rays to destroy the cancer cells, with as little damage as possible to the surrounding healthy cells. It is usually done externally using a special computerised tomography (CT) scanner, however is sometimes done internally using a bronchoscope, for example when a tumour is blocking one of the airways. This also has severe side effects, such as chest pain, fatigue, severe coughing and hair loss.

Future Diagnostics

Nanotechnology could revolutionise this whole process. There has already been a lot of research into nanotechnology's possible role in oncology, however I believe the most important area is the early detection of cancer, as if it is detected before it has metastasized then the prognosis is much better with roughly 70% of patients who are diagnosed early, being able to survive for at least 5 years, National Cancer Institute (2005).

Currently, doctors use computed tomography scans, in the detection of cancer by measuring the diameter of the nodule using the RECIST method. However, scientists at the National Institute of Standards and Technology (NIST), found that by measuring the volume of the lymph nodes, using three dimensional analysis, they should be able to notice volume changes up to ten times smaller thus reducing the diagnosis time from six months to four weeks, which can be vital in a patient's prognosis. The great thing about this, is that it would be simple to implement after all three dimensional diagnostic images can already be taken. However, Levine warns that not all tumours are elliptical pill shapes, therefore this data will not apply to those, however the majority are.

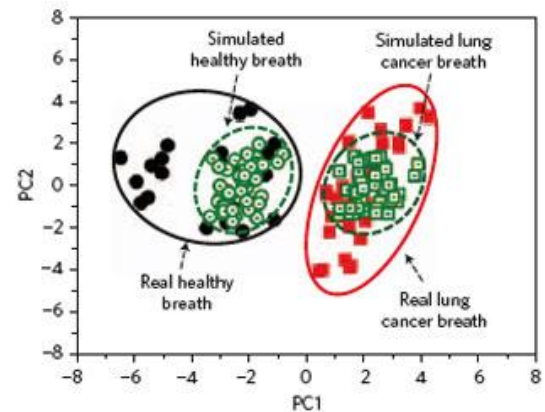


Figure 7

A revolutionary breath analyzer is currently being developed in Israel, that uses a network of carbon nanotubes to analyze the patients breath and can distinguish between lung cancer

patients and healthy patients, with more than 86% accuracy. This is an extension to the trial in 2006, which found that dogs could smell cancer on the breath of patients, with an amazing 99% accuracy. It does this by using a variety of chemiresistors based on functionalized gold nanoparticles combined with a pattern recognition function. Haick developed a system using five volatile biomarkers of lung cancer, which could not only diagnose lung cancer but also identify types of primary lung cancer. If this could be developed further it would be truly innovative as it could be an economic, portable device for widespread screening. Potentially, this could save millions of lives by catching cancer in a routine check up, which is especially important in lung cancer as often the symptoms are dismissed as a smokers cough. This method could also possibly be extended to use with 'fresh' biopsy samples, where a speedy dichotomic diagnosis would be vital to surgeons, Haick (2009).

This led me to thinking of the possibility, in the distant future of a nanodevice which encompasses this breath analyzer permanently fitted into the patient's mouth or trachea, via a tooth etc, which could be checked by a general practitioner at regular intervals, or wirelessly send alerts to the GP when certain volatile organic compounds are detected at high levels in the breath. This would have to be on a nanoscale to avoid discomfort to the patient, therefore truly encompasses the idea of a miniature 'biological computer'. However, this poses huge ethical issues as many people objected to the government establishing a 'DNA database' through the identity card system, penultimately leading to the idea being scrapped. On the other hand, if it was a voluntary system then I believe huge numbers of people would agree to it, especially those who have been personally affected by cancer.

Furthermore, mutated cells could possibly be detected before they form a tumour. Scientists are currently developing a way to detect tumours at an earlier stage. Quantum dot molecular imaging, allows us to see biological processes within cells, thus we should be able to detect pre-cancerous cells, using this method scientists were able to observe the lymph nodes on mice for over 4 months. Quantum dots are so effective as they are 20 times brighter and 100 times more stable than traditional fluorescent reports. In theory we should be able to do this on patients by injecting them with quantum dots of varying colours, which would effectively label cancerous cells via a PET scan. In addition to this scientists have made their first attempt to use quantum dots for tumour targeting, in animals. There are two methods of doing this passive and active targeting; passive is based upon the tumours permeable membrane and ineffective drainage system, active targeting allows the quantum dots to have tumour-specific binding sites, to selectively bind to tumour cells.

Ethical Issues

As previously mentioned in my introduction Drexler, coined the term grey goo, which has since featured prominently alongside all successes in nanotechnology, with nanobots even featuring in Hollywood blockbusters, with films such as Agent Cody Banks (2003) telling children nanotechnology is a 'villain', as well as dignitaries such as Prince Charles (2004) predicting that

the world will be overrun by 'grey goo' nanomachines. Therefore, undoubtedly if lots of nanomedicine products appear, people will be worried as they believe they are putting something very intelligent therefore 'potentially dangerous' into their bodies.

In addition to this there is the continuous problem in medicine of proving something is 100% safe, and in science nothing is final. Every product entering the nanomedicine market has to undergo rigorous testing, to avoid disasters like the thalidomide affair, many will be eliminated during these stages and those that manage to get through will only do so after roughly 10-15 years of trials. Regrettably, long nanofibres which have previously been hailed as one of nanotechnology's marvels were able to cause inflammation and scarring in the mesothelium of mice. This damage was very similar to the pre-cancerous damage caused by asbestos, however this is not the end for nanofibres, as this is only one trial, on mice not humans and they are surrounded in a protective coating on most consumer products.

This leads onto the next ethical issue of animal testing, many people consider it a necessary evil in order to progress in medicine, however there are people who strongly disagree with animal testing and will go to extreme lengths to demonstrate this view. Therefore, for a product to even reach this stage it needs to be feasible and worth the risk to the company and scientists involved.

CONCLUSION

In conclusion, Nanotechnology has the potential to revolutionise medicine, however it is limited by the necessary 'health and safety' nature of medicine, therefore I believe it will be seen on mass in many other fields before medicine. Particularly, as most of the research in this paper is either theoretical or has not yet reached clinical trials.

However, there is already exciting research going on, especially in oncology, such as Haick's work on diagnosing cancer simply by analyzing someone's breath. That's one of the reasons I decided to develop this paper on diagnosis, as I believe early diagnosis is the key step to beating cancer. In addition to this I chose to write about lung cancer, as it is the biggest cancer killer in the United Kingdom, mainly due to it often being diagnosed once the cancer has metastized.

I believe, that nanotechnology is the key to beating cancer, however it has limitations (as previously discussed), particularly with peoples science fiction fears of what nanobots could be capable of. In addition to this, I believe oncology will be the key area that nanomedicine features, as 1 in 3 people will develop some form of cancer, Cancer Research UK (2008), therefore vast amounts of money are being spent by many organisations into finding a cure, which is needed to fund nanotechnology research.

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