

Nanoxray treatment using Nbtxr3 nanoparticles as an alternative to radiotherapy for the treatment of cancer, the way in which this impacts the future of the healthcare and the ethics of nanotechnology research.

By

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PASS WITH MERIT

RESEARCH PAPER  
BASED ON  
PATHOLOGY LECTURES  
AT MEDLINK 2010

## **Abstract**

Nanotechnology is at the forefront of science in present day research. It offers a whole new horizon of treatments, therapies and imaging that is impossible with other larger scale techniques. One area of medicine that is currently developing the revolution of nanotechnology to its advantage is oncology and cancer treatment research. New and exciting ways of treating cancer are being developed including the technology that our report is based on; Nanoxray, involving Nbtxr3 nanoparticles. Nbtxr3 particles can be activated in cancer cells and cause them to self destruct, leading to a new viable, less-invasive and efficient generation of cancer treatment. In this paper we will discuss the ethical implications of nanotechnology as well as its role in revolutionising healthcare.

## **Introduction**

Nanotechnology has been the source of many recent scientific advances. This is due to its staggering approach not only to the medical field but other day to day uses. Its accelerated growth in society has led to a whole new perception of how important nanotechnology could be for our future. Although it has been previously addressed as morally wrong, its ends have justified its means.

*“As far as I can see, do not speak against the possibility of manoeuvring things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big.”* — Richard Feynman, Nobel Prize Winner in Physics.

Nanotechnology is a branch of science and engineering, devoted to the design and production of materials, structures, devices and circuits at the smallest achievable scale, typically manipulating matter atom by atom. To put into scale how small a nanometre is, try imagining the diameter of a human hair, measuring 200,000 nanometres. Nanotechnology has been applied to many areas of research and development from medicine to engineering, manufacturing, computing and even to cosmetics and textiles. This technology has been around for many years, but through current research and development it has recently become known, due to its news breaking advances. A major use that stole the spotlight is the development of the Buckminsterfullerene, otherwise known as ‘buckyballs’ or ‘fullerene’. This is a spherical molecule consisting of 60 carbon atoms that is used to counteract free radicals within the human body. Free radicals are known to lead to cancer within humans and therefore buckyballs are used as antioxidants to counteract these, preventing the probability of the development of cancer <sup>[1]</sup>. Other uses of nanotechnology consist of normal uses in everyday situations such as in sunscreens, self-cleaning glass, clothing, scratch-resistant coating, swimming pool cleaners and disinfectants <sup>[2]</sup>. New products that incorporate nanotechnology are being released every day. These advances help us extremely in the medical field by cutting out the risks and side effects that occur due to current treatments, thanks to the scale at which these nanoparticles work at. A major

area of nanotechnology is perfecting drug delivery to specific, targeted cells and tissues. This can be through the use of nanotubes, which too, work in the same manner as buckyballs, in terms of transporting drugs. Also under development is the invention of nanobots which aim to repair cell damage and mimic cell functions.

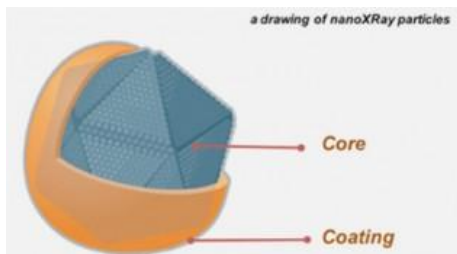
Research into nanotechnology is currently receiving enormous amounts of funding from many governments and organisations, for example the EU Seventh Framework Programme will be contributing approximately €600 million per year until 2013 <sup>[3]</sup>. Because a great amount of money is being invested, it is only feasible if the benefits of this research are applied to an area of medicine that itself requires a lot of funding to sustain and reduce treatment costs. This way nanotechnology can provide new ways of addressing the problem and producing more efficient and cost effective ways of managing conditions. The area of healthcare that we propose would benefit from this rearrangement of funding would be cancer treatment. Cancer is an area which is an increasingly huge financial difficulty for the NHS. Data from the Office for National Statistics (ONS) and other peer-reviewed published sources show that the cost of cancer in 2008 amounted to a total of £18.33 billion and these costs are said to increase to £24.72 billion by 2020 <sup>[4]</sup>. These increases in financial cost for the NHS are huge burden and due to the expectations of the rates of cancer increasing, costs will escalate further. The application of nanotechnology to cancer care can develop more efficient treatments, reducing the long term costs of the treatment of patients.

All cancers develop in body cells, caused by the DNA within the cell becoming damaged or changed. This leads to mutations within the cells which then affect the normal cell growth and division (mitosis). When this occurs cells do not die but rapidly and uncontrollably divide, even though the body does not need them. These extra cells can then go on to form a mass of tissue known as a tumour; these can be benign (meaning they are not cancerous) or malignant and therefore cancerous. Some cancers may not be caused by tumours, such as leukaemia which develops in the blood and bone marrow <sup>[5]</sup>. Deaths from cancer are continually rising, with an estimation of 9 million people dying in 2015 and 11.4 million people in 2030 <sup>[6]</sup>, therefore effective treatments are needed. In the UK one in three people will develop cancer at some point in their lives <sup>[7]</sup>. The main current treatments that are implemented are; chemotherapy, radiotherapy, surgery, biological therapy, hormone therapy, biphosphonates and transplants. However, with each of these there are major side effects, radiotherapy in particular. There are a variety of effects radiotherapy may have on people. Lethargy and tiredness is a common side effect experienced, especially if treatment is extended over many weeks. This could be a result of the body repairing the damage which had been caused to healthy cells or by the shortage of red blood cells (anaemia). Further possible effects may include weakness, soreness of skin and hair loss in the treated area <sup>[8]</sup>.

## Discussion

### The medical potential of Nanoxray

The proposed new treatment for cancer is in the form of Nanoxray – a recent development of nanotechnology. The core of the Nanoxray nanoparticle is an inactive and inert substance (Nbtxr3).



“The core of the Nanoxray platforms Nbtxr3 is a dense, biocompatible nanoparticle (see figure 1) designed to infiltrate only the targeted tumour’s cells”<sup>[9]</sup>. Nbtxr3 nanoparticles enter malignant cells via endosomes (membrane bound vesicles found near the plasma membranes of cells) by the process of endocytosis.

Figure 1<sup>[9]</sup>

Nbtxr3 is not a drug as it doesn’t actively react with any cell contents. After Nanoxray nanoparticles accumulate in the targeted tissues (the tumour), x-rays from an external source generate a local therapeutic effect (intratumourally). The physical and energetic action mechanism of the Nbtxr3 particles is based on the creation of free radicals and heat generation after a standard dosage of x-rays are absorbed by the particles within cancer cells in vivo. This activates the particles by x-rays (protons and electrons) being absorbed, in the same way that ionising radiation is absorbed by water molecules, to create oxygen free radicals. In both of these circumstances x-rays generate high kinetic energy electrons that are then released into the cytoplasm of the cancerous cells, and will then generate oxygen free radicals and a sufficient amount of heat energy. These oxygen free radicals are extremely reactive and trigger all different types of damage to the membranes, proteins and nucleic acids inside the cancerous cells<sup>[10]</sup>. This damage leads to biological consequences within the tumour cells, which includes cell inactivation and lethal processes. Effectively the cancerous cell will start to enter a “self destruct” mode as the damage (especially when DNA is disrupted) is too difficult to repair effectively so therefore terminates its own cell life. This is referred to as apoptotic cell death program. This therefore creates a higher ratio of damage between malignant cells and healthy somatic cells, reducing (if not eliminating) tissue damage and the side effects of conventional radiotherapy.

Conventional drugs would be too big for effective cell penetration and particle dispersion. However Nbtxr3 nanoparticles are 70nm in diameter (see figure 2) so wouldn’t experience this problem and be able to cause maximum damage to cancer cells.

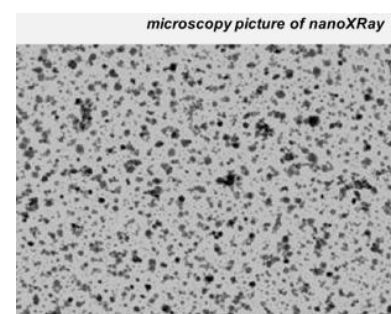


Figure 2<sup>[9]</sup>

Stability in biological media is achieved by coating the nanoparticles with a surface-treating agent. This is biocompatible and helps ensure that the nanoparticles are stable within the physiological fluids, thus reducing the chances of the particle being rejected or affected by other metabolic reaction and organic compounds found inside the malignant cells. The Nbtxr3 nanoparticles consist of many characteristics including low surface area due to their spherical shape. This is a favourable morphology which enhances cellular penetration <sup>[9]</sup>.

When x-ray irradiation is not present the nanoparticles return to their inactive state, stopping the process of production of more oxygen free radicals and keeping the action of the free radicals local to the malignant cells. This allows for the process to be repeated several times using the same nanoparticles, reducing the amount of units that need to be manufactured. Recycling them reduces the amount of time spent administering the particles and will make repeat treatment of the tumour for a number of sessions more efficient, ensuring the patient a better service. The fact that the particles can also be controlled and their ability to cause damage halted means that this method is a very controllable and feasible treatment of malignant tumours, even in the most delicate areas of the body or in tumours which are more difficult to treat conventionally <sup>[10]</sup>.

### Preclinical studies

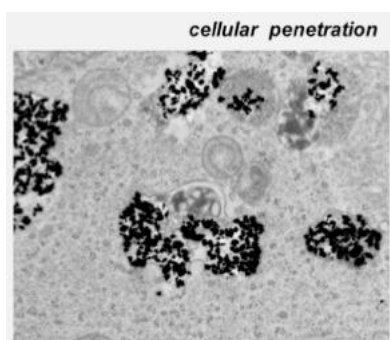


Figure 3 <sup>[11]</sup>

There have been many pre-clinical trials carried out involving the Nbtxr3 nanoparticles. The first of which was to test the uptake of Nbtxr3 into tumour cells. Nbtxr3 has been demonstrated to be taken up by mammalian cancer cells (see Figure 3). To confirm that the cellular uptake of nanoparticles is mediated through endosomes, transmission electron microscopy (TEM) has shown particles in the dark patches, which are very successfully taken up by cancer cells but not healthy somatic cells <sup>[11]</sup>.

The performance of Nbtxr3 was also tested by measuring the cell viability of 2 samples of cells after 24 hours; one with the Nbtxr3 particles inside the tumour cells and one without as a control sample. They were then both exposed to varying levels of irradiation (up to 6 Gy). The results showed that Nbtxr3 used in combination with radiotherapy was far more effective at destroying cancer cells. As shown

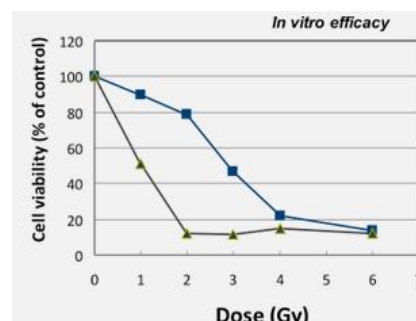


Figure 4 <sup>[11]</sup>

in Figure 4, 1 Gy of irradiation with the use of Nbtxr3 particles and radiotherapy corresponds to efficacy of 3 Gy of irradiation without any Nbtxr3 particles using radiotherapy alone <sup>[11]</sup>. This evidence

proves that Nbtxr3 nanoparticles successfully reduce cell viability when exposed to irradiation to an equal extent of three times the irradiation without the particles, meaning that lower doses of irradiation in the form of x-rays would have to be administered in order to achieve the same maximum effects. Also this significant decrease in the amount of irradiation needed for the same effects would also mean that there would be less damage caused to healthy cells and there will be more damage to the cancerous cells exclusively.

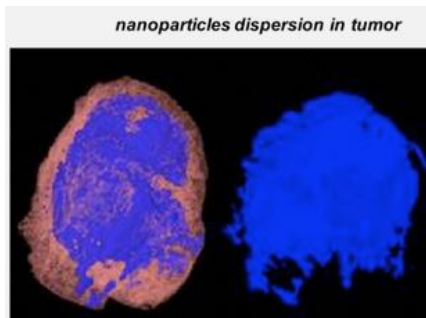


Figure 5 <sup>[11]</sup>

The intra-tumour use of Nbtxr3 particles was also tested by injecting mice with a dose of the nanoparticles intratumourally. As shown in figure 5, after a period of 15 days post injection the particles (shown in blue) are well dispersed throughout the tumour and are present in a wide spread of the cancerous cells.

A performance study of Nbtxr3 was also carried out in HCT116 tumour models. Nbtxr3 had been injected intratumorally into mice bearing tumours on their flanks. Local irradiation of tumours had been performed and in mice injected with Nbtxr3 a total regression of tumours on all mice was observed compared to 5% in glucose-treated mice that received radiotherapy alone. After 60 days, 90% of animals were still tumour free when treated

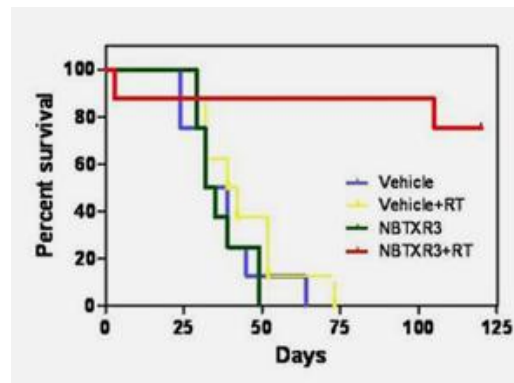


Figure 6 <sup>[11]</sup>

with Nbtxr3 and radiotherapy combined. The group of mice who had received radiotherapy alone had shown re-growths of the tumours <sup>[11]</sup>. This shows that not only is using the nanoparticles more effective and energy saving it also prevents re-growth of tumours better than current cancer therapies alone. Employing the use of Nbtxr3 on all cancer patients would result in a huge majority of patients not needing to receive secondary treatment, reducing the amount of money that needs to be spent by the NHS in the long term on treating cancer recurrences. This would be particularly crucial when dealing with certain types of cancers such as rectal cancer as approximately 23% of rectal cancer patients experienced a recurrence within five years <sup>[12]</sup>. Considering this high incidence of re-growth, it seems the natural step forward to use these nanoparticles to reduce these statistics, saving valuable NHS funding and time whilst increasing the survival rates from some forms of high incidence of recurrence cancers.

Research has also been carried out into the systemic tolerance of Nbtxr3. The tolerance of HCT116 tumour bearing mice to repeated doses of Nbtxr3 was explored. This allowed

potential toxic effects of the Nbtxr3 to be explored after exaggerated injections compared to the planned one-injection use in humans<sup>[11]</sup>. No traces of the nanoparticles were found in urine and they were eventually excreted in faeces with no toxic properties observed.

### Ethics of the use of nanotechnology in medicine

It is clear that the development of nanotechnology in medicine is the new revolution, but is there a potential pit fall to the newly discovered wave of nanotechnology? In a sample of 1,015 adult Americans, only 29.5% of respondents agreed that nanotechnology was morally acceptable<sup>[13]</sup>. Do they have their reasons for being so sceptical about the nano revolution?

The advancement of nanotechnology could lead to people living extremely long lives due to the lack of disease and availability of treatments. This could cause problems of overpopulation of the world and therefore huge food shortages and a lack of land to house people, resulting in increases in poverty and therefore of cramped conditions with poor nutrition. The spread of disease may be more affluent despite the advances in medical technology and treatments under these inhumane conditions. Also at what point would you have to stop people from having children to reduce overpopulation? Surely this will impact significantly on people's human rights and free will. Also it would put huge power in the chemical engineers' hands that discovered this and would cause exploitation of technology for their own personal gain and not for the gain of the population, possibly resulting in huge inflation of prices for nanotechnology and the companies who develop it effectively "playing God".

However nanotechnology could also be used to develop new ways of cleaning water in third world countries to eliminate water-borne diseases such as cholera or dysentery, which is currently a problem in populations such as Africa. Solving these fundamental problems would lead to a better quality of life for many people. However it is more than likely that the western and more privileged world will become oblivious to these selfless possibilities and be blinded by nanotechnology's smokescreen of awe. Ideas such as using nanotechnology for the improvement of technology and gadgets such as supercomputers and batteries that can last for months could distract researcher's attention in a quest for corporate wealth. It is human nature to be greedy and want to take advantage of opportunities such as these for commercial gain. Will people of the west even consider people in Africa who are dying preventable deaths amongst this newfound greed?

With the current fragile political climate in countries such as Libya, there is the possibility that nanotechnology could potentially be used as a form of bioterrorism or a biological weapon in modern warfare. Many people are well versed in the use of anthrax in biological weapons and how it was found to be extremely dangerous as it could be made into anthrax bombs and spread out across great areas. Using nanotechnology, new biological threats could be used in warfare such as the use of nanobots to cause havoc in somatic cells and

damage nerve cells using other nanoparticle drugs. This has not yet been developed yet could be a possible threat as research and knowledge of nanotechnology increases. Once the revolution has started, it may become easy to synthesise and abuse technology like this. This could prove a potentially devastating effect on millions of people and involve innocent civilians becoming deliberately harmed by terrorism even more so than today.

Another factor to consider could be the possibility of pollution due to nanoparticles such as Nbtxr3 accumulating in the environment. Although the use of nanoparticles in medicine is an undeniable breakthrough, we must appreciate that if they are being excreted by patients on a large scale what effect will this eventually have on the environment? If they circulate in sewage plants how will they be removed and not leave any pollution, especially seeming as the particles are technically medical waste?

However it is important to remember that even though the development of nanotechnology could potentially cause ethical issues, one must consider the fact that it will also save many lives in addition, improve the quality of life for many people and finally revolutionise the way that healthcare is administered and developed.

#### Developments of the treatment

It is suggested by the company Nanobiotix™ that they plan to inject the particles intratumourally, however during clinical trials the best results may be from patients who received the particles intravenously or otherwise, so therefore a change in the planned method administration may be required. An oral administration could also be developed in the future using nanotechnology drug delivery systems currently being developed. This could potentially add to the ease of administration of the drug, though this may not be necessary due to the fact that the particles can be reactivated and are not for use as a long-term drug to be taken at home.

Also current cancer treatments such as radiotherapy and chemotherapy can only be employed on local tumours. However, Nbtxr3 could be developed in the future to treat cancers that have undergone metastasis and have become lymphatically or hematogeneously spread. If a new intravenous method of administration could be developed the particles could be developed to seek out and destroy cancer cells, even after they have spread to other areas of the body. This could help save many lives in currently terminally classed cancers.

#### The future for healthcare services in the managing of cancer and how Nbtxr3 nanoparticles will help

It is clear to see that our society in the UK is ever changing. Attitudes, cultures and population patterns have altered dramatically in the past millennium and are projected to

continue doing so across the decades. One of the most significant changes predicted to come is the change in the general age of the population. In the UK, it is projected that the proportion of the population aged 65 and over will rise from 16% in 2009 to 23% in 2035 <sup>[15]</sup>. Also in 2009, the proportion of the population aged 65 and over was under one fifth for most European countries; by 2035 the average proportion of the population aged 65 and over across the 27 EU countries is projected to rise to a quarter <sup>[15]</sup>. This huge increase in the proportion of elderly people in the UK and Europe will mean that the NHS will have to re-evaluate the ways in which healthcare is currently managed and distributed. In the years to come the UK is likely to see an increase in the rates of illnesses that affect elderly people predominantly, such as arthritis and cancer. The rise in the number of elderly people will eventually lead to the increase in cancer diagnosis statistics, therefore the NHS will need to consider ways of treating cancer more effectively and diagnosing it earlier to improve survival rates and save costs. An ideal way to tackle this issue is to employ the use of nanotechnology such as Nanoxray to increase the efficiency of cancer care for the growing elderly population as well as developing nanotechnology to improve medical imaging to enhance diagnostics.

Also a point to consider for the future of medicine and cancer care is that there has been an increase in recent years in the number of teenagers starting to smoke. The report from the Schools Health Education Unit shows trends in young people's attitudes to smoking between 1983 and 2001. The findings reveal that 40 per cent of 12 to 13-year-olds admitted they had tried cigarettes in 2001. This rose to 60 per cent among 14 to 15-year-olds. That compares to 30 per cent of 12 to 13-year-olds in 1990 and 57 per cent of 14 to 15-year-olds <sup>[16]</sup>. From these statistics it could mean that the UK may well see a substantial increase in the amount of people diagnosed with lung cancer in particular in the next 20 to 30 years (the period of which it can take for lung cancer to develop as a result of continuous smoking). This would also call for a more efficient way for cancer to be treated as to not cripple the NHS in terms of time and budget.

As previously discussed in the pre-clinical studies section of this paper Nanoxray treatment requires less irradiation to perform effective results compared to conventional radiotherapy. This would decrease the amount of money that the NHS would have to budget for cancer treatments in the long run as up to a third of the energy used for current radiotherapy procedures will have to be employed. This saved money could be invested into the distribution of current drugs for all diseases that some areas of the country are deprived of due to the postcode lottery system, which is currently unfair to some people in need of treatment who may not live in correct area to receive their medication under NHS provision.

## **Conclusion**

Because of the complex nature of cancer and our still being unsure on how to repair damage to DNA in cells, it can be said that it is much more likely and beneficial for the mean time that we develop better and more effective treatments. Using nanotechnology as a starting point for these treatments is necessary, as it is time for a new perspective on cancer management. Nanotechnology is arguably the future of medicine and Nanoxray is leading that innovation. Significantly reducing the damage to healthy cells and reducing side effects for patients is undeniably a breakthrough. However Nbtxr3 particles have yet to be tested in clinical trials so their direct effect on humans hasn't been observed. When mice were injected with doses larger than the intended single dose proposed to be given to humans <sup>[11]</sup> no side effects were recorded <sup>[11]</sup> so this is a good indicator that there will be few or no problems when given to humans. However it is impossible to know for certain if there are any side effects to the treatment until substantial clinical trials have been carried out. All in all nanotechnology unlocks a new world of science waiting to be explored and maybe one day it will reveal that sought after Holy Grail – a cure for cancer. Medicine is changing. The future is nano.

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