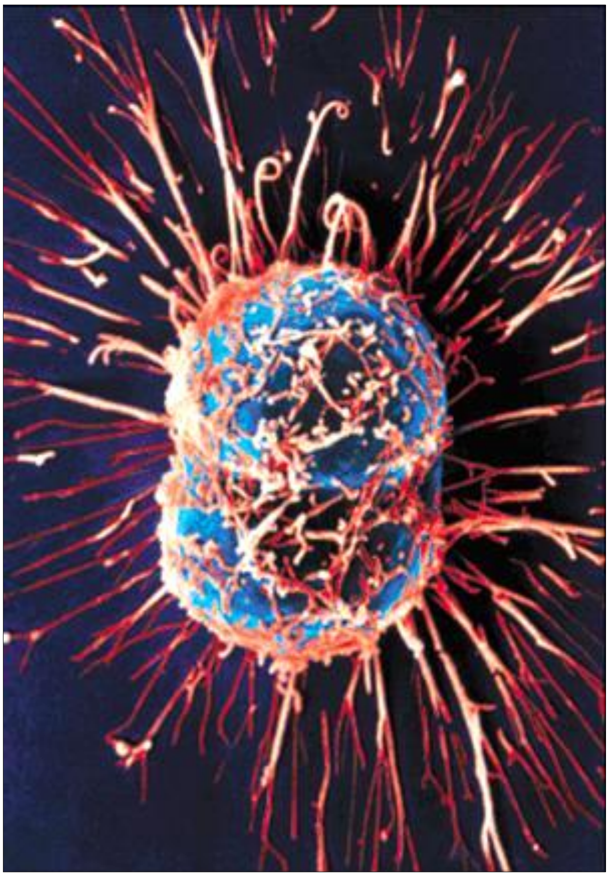
NANOTECHNOLOGY:
THE FUTURE SOLE CURE FOR CANCER?



By
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PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2010

Abstract

Cancer is often a terminal disease which affects thousands of people every year; '*in 2007 , 297,991 people were diagnosed with cancer*'**[1]** in the UK alone. Although there are many different methods for the treatment and prevention of cancer, e.g. chemotherapy and radiotherapy, none of these methods have been able to finitely cure cancer, and all have their own side-effects, risks, levels of accuracy and survival rate. Nanotechnology (the science of microscopically small molecules) has the potential of finally eradicating this horrific and widely diverse disease; for instance, recent research into nanotechnology has exemplified the possibility of robotic interfaces that respond directly to cancerous cells. Nonetheless, like any new research, there is a great deal of speculation surrounding nanotechnology. This dissertation will examine the potential role of nanotechnology in the treatment of cancer, as well as any problems or risks it could pose.

Introduction

Nanotechnology is the study into the manipulation of atomic and molecular matter, thus, it constructs and develops structures sized between 1 nanometre and 100 nanometres – just to put this into context, a nanometre is equivalent to one billionth of a metre and approximately ten atoms fit inside one nanometre (as illustrated by Figure 1).

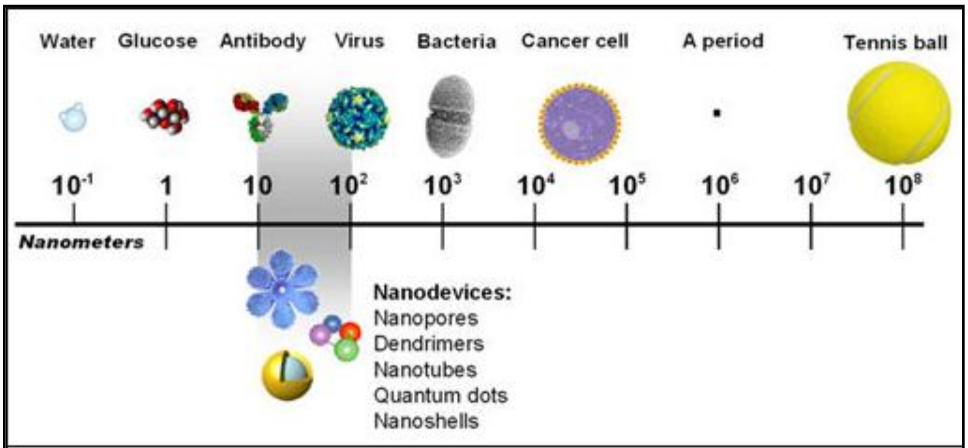

Figure 1 - Diagram to illustrate size of a nanometre

The term 'nanotechnology' was generated by Professor Norio Taniguchi and Eric Dexler in 1974 and has since become a popular buzzword, but the actual concept of manipulating atoms and molecules was primarily considered in 1959, by Richard Feynman. Nanotechnology took off in the 1980s, due to the rise and understanding of cluster science as well as the invention of the STM (scanning tunnelling microscope). This was then followed by the discovery and manipulation of fullerenes in the mid 80s.

Nanotechnology is now being applied to almost every field imaginable, from electronics to optics, to materials development and to biomedicine, involving scientists from many different disciplines. Nanotechnology has begun to give rise to impressive scientific developments in many areas, such as protein synthesis, micro-computing and molecular engineering. It also incorporates the creation of tools and processes at the atomic level that will facilitate the synthesis of various materials and structures.

Nanoscale devices are perfectly adapted to interact with biomolecules on both the surface and inside of cells, because of their small size. They can therefore; readily gain access into so many areas of the body, rapidly detect disease and deliver treatment in ways unimagined before now.

In order to present a dissertation on the future finite treatment of cancer with nanotechnology, the cancer-combatant devices that have already been produced must first be understood. There are thousands of examples of these 'specialized' nano-structures and devices, many of which are utilized to combat cancerous cells, e.g nanowires, nanoshells and nanoscale cantilevers.

Nanowires consist mainly of carbon and silicon, and are incredibly thin, man-made constructs; they can range from having a diameter of one to sixty nanometres! Nanowires are used to detect the presence of altered genes associated with cancer, thus they can enable researchers to pinpoint the exact location of those changes. The nanowires are laid down across a microfluidic channel and as particles flow through this channel, the nanowire sensors pick up the molecular signatures of these particles and can immediately relay this information through a connection of electrodes to the outside world.

In December 2009, Yale researchers made a breakthrough in the detection of cancer as they developed a new method of recognising cancer biomarkers in the blood for breast and prostate cancer, by measuring the concentrations of two biomarkers for the cancers with nanowire sensors. Before this development, nanowires had only worked in controlled, laboratory settings, but the researchers proved that these sensors could be used in 'whole' blood, even though the blood is a highly '*complicated solution containing proteins and ions and other things that affect detection.*'**[2]** By utilizing these nanowire sensors, the Yale researchers were able to detect the antigens specific to breast cancer and prostate cancer, with a ten percent accuracy in concentrations as low as 1 picogram (1 trillionth of a gram) per millilitre.

Nanoscale cantilevers are microscopic, flexible beams, which resemble a row of diving boards! (see Figure 2) These 'diving boards' are built using semiconductor lithographic techniques and can also be adorned with certain molecules that are capable of binding specific substrates; for example DNA strands that are complementary to a specific gene sequence or antibodies.

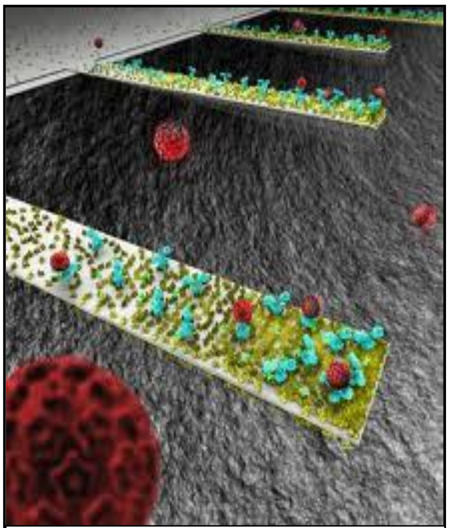

Figure 2 – cantilevers recognising cancer cell secretions

Micron-sized devices, comprising of many cantilevers, can detect single molecules of DNA or protein, subsequently, as a cancer cell secretes its molecular products, antibodies that have been coated on the cantilever 'fingers' selectively bind to these secreted proteins (as shown by Figure 2). The physical properties of the cantilevers change as a result of this binding, as the antibodies will have been designed to pick up one or more different, specific molecular expressions from a cancer cell. Researchers can read this change almost instantly and provide not only information about the presence and the absence of the different molecular expressions but also their concentration. Nanoscale cantilevers, constructed as part of a larger diagnostic device, can provide rapid and sensitive detection of cancer-related molecules.

On the 30th August 2001, the journal Nature Biotechnology published a report on a newly developed microchip that was able to '*detect the first signs of prostate cancer'* **[3].** The microchip functioned by inducing proteins, produced by prostate cancer cells, to stick to and bend a microscopic cantilever; the higher the concentration of the protein being measured, the greater the deflection of the cantilever and the cantilever was so accurate it could detect these proteins at levels 20 times smaller than those produced by prostate cancer. This ricochet of the cantilever was then measured using a laser. The Berkeley research team who carried out this study had also found a way to put several hundred cantilevers onto a single silicon chip, making it possible to test patients for many different chemicals/proteins/DNA molecules at one time.

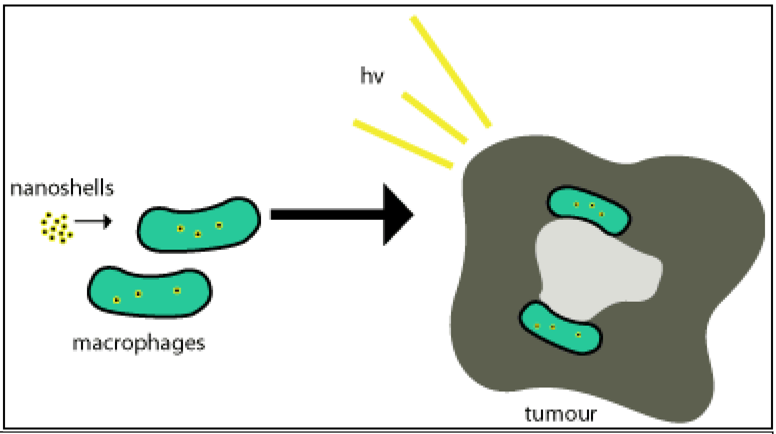

Figure 3 - Diagram illustrating how nanoshells can be used to terminate tumour cells

Nanoshells are a type of spherical nanoparticle consisting of a dielectric core, often silica, which is covered by a thin metallic shell (usually gold). Due to their microscopic size, these nanoshells can invade tumour cells through the use of phagocytosis; the phagocytes engulf the nanoshells through their cell membrane to form an internal phagosome, or macrophage.

Scientists can ensure that the macrophages solely 'invade' the tumour cells and not any neighbouring healthy cells by further decorating the nanoshells to carry molecular conjugates to the antigens that are expressed on the cancer cells themselves or in the tumour microenvironment. In order for these nanoshells to effectively 'treat' the tumour, they just need to be within the tumour cells, as nanoshells possess highly favourable optical and chemical properties; these properties allow the scientists to accurately determine where the tumour is exactly and then near-infrared illumination is used to solely terminate the tumour cells; this is otherwise known as photo-induced cell death. This method of utilizing nanoshells is shown in Figure 3.

Nanoshells have been the subject of a great deal of successful research recently, especially in conjugation with cancer treatment/diagnosis. For instance, an investigation into the utilization of nanoshells was executed, in April 2010, by researchers at Ohio State University, who were endeavouring to develop a successful method of diagnosing glioblastoma tumours (Glioblastomas are generally found in the temporal, or frontal lobe of the brain, and tumours located there are difficult to see and remove.) with the help of different nanoparticles. The focus of the Ohio researchers was to combine two different particles together so that the outcome would have multiple properties in one small particle known as *'nanocomposite'*[**4**] ; in the study published in the journal Nanotechnology, the researchers claimed that they were successful in doing so! The study stated that the researchers had successfully fabricated a nanocomposite that has magnetic and fluorescent properties and is less than 20 nanometres in size. The magnetic feature would enable scientists to diagnose cancer cells with MRI more accurately and precisely whilst the fluorescent feature would allow them to see the tumour under UV light. Combining two different particles' properties is a difficult task and it had never been previously attempted before; the researchers hope that this new development will help doctors in treating the lethal brain disease glioblastoms.

Discussion of possible future developments of nanotechnology

Recently, nanotechnology has been proven to be a highly effective method of cancer treatment/diagnosis, due to numerous successful studies undertaken in the past few years, some of which were mentioned in the introduction. However, is there any real possibility of nanotechnology ever becoming the established, finite cure for cancer, and replacing the 'traditional' treatments such as chemotherapy and radiotherapy? The incredibly rapid rate at which nanotechnology has been developing suggests that this speculation could become reality quite soon.

On 3rd March 2009, the journal Cancer Research published the findings of an investigation into *'Cancer-Specific Transgene Expression Mediated by Systemic Injection of Nanoparticles'* **[5]**, and although this study had been solely executed in mice, the researchers said that they were endeavouring to continue this study with human trials in 2011, thus providing a cure for metastatic tumours. These findings would have been seen as 'Star Trek' science and it would have been considered impossible to execute such an experiment just a few years ago!

In order for the nanoparticles to be effective against the cancer, the ideal anti-tumoral agent had to be able to target malignant cells throughout the body whilst sparing normal tissues, and so far cancer gene therapy has been restricted due to the lack of systemically active, cancer-specific delivery vectors, especially in the field of non-viral, synthetic gene delivery vectors. The nanoparticles were composed of polypropylenimine dendrimers of third generation (PPIG3), so when combined with DNA, they were truly capable of efficient gene transfer to tumour deposits, upon systemic injection. Significantly, when a therapeutic transgene was used, marked anti-tumour activity was observed, leading, in some experiments, to the “cure” of all the mice that were treated!

In their study, the researchers exemplified a tumour-specific gene transfer on systemic injections of nanoparticles of dendrimers in tumour-bearing animals. Through the employment of nuclear whole-body imaging and NIS as a reporter gene, they were able to detect a specific and unique radiotracer uptake in tumours of both the immunodeficient and immunocompetent mice, whereas no signal was detected in normal tissues of the animals. A NIS-specific RT-PCR signal was detected in the tumour sites, whereas no signal above the detection threshold was observed in the kidneys, livers, spleens, hearts, and lungs, all of which are known to retain non-specifically synthetic or viral particles from earlier investigations; for instance, the 2004 study into *'Biodistribution and targeting potential of poly(ethylene glycol)-modified gelatine nanoparticles in subcutaneous murine tumour model'* **[6]**.

Importantly, quantitative RT-PCR on differing organs obtained at the autopsy of the scanned mice presented the same conclusions. The biodistribution of the nanoparticles was indirectly measured by quantitative PCR on DNA, which had been extracted from various tissues, 24 hours after the first systemic injection. There wasn't a single trace of NIS plasmid DNA detected in the stomach, thyroid, kidney, and bone marrow, whereas a weak but detectable signal was measured in the liver, spleen, and lungs. In the tumour, this signal reached 20-fold that of the liver, suggesting a 'positive' accumulation of the nanoparticles in the malignant lesion.

This accumulation property appears to be exclusive to the PPIG3/DNA nanoparticles because synthetic vectors are usually agglomerated in abundance in the lungs, kidney, and liver 1 hour following administration and are generally still detectable for up to 3 days. Consequently, this extratumoral accumulation can induce severe toxicity, thus presenting a reason as to why its applications are still limited in humans. By contrast, the researchers observed that there was no loss of animal body weight or signs of long-lasting or serious toxicity upon and after the systemic injection of the PPIG3/DNA nanoparticles.

In context of systemic delivery, molecular imaging provides a whole-body, minimally invasive method of transgene expression. The information obtained by in vivo molecular imaging revealed that PPIG3/DNA nanoparticle–mediated gene transfer in tumours was ephemeral and that it obtained its maximum 'peak' just 24 hours after administration. Thus, considering that NIS imaging of transgene expression has recently been lawfully sanctioned for use in humans, this highly successful investigation has illustrated the full capability and potential of these nanoparticles as a new vector for cancer gene therapy. If plasmids with a therapeutic expression cassette (a cancer-cytotoxic cytokine that would diffuse through the tumour) were utilized, combined with an imaging expression cassette (in which NIS expression is driven by a strong, ubiquitous promoter), this form of nanotechnology may provide therapeutic benefits for patients with metastatic tumours and even a finite cure for cancer.

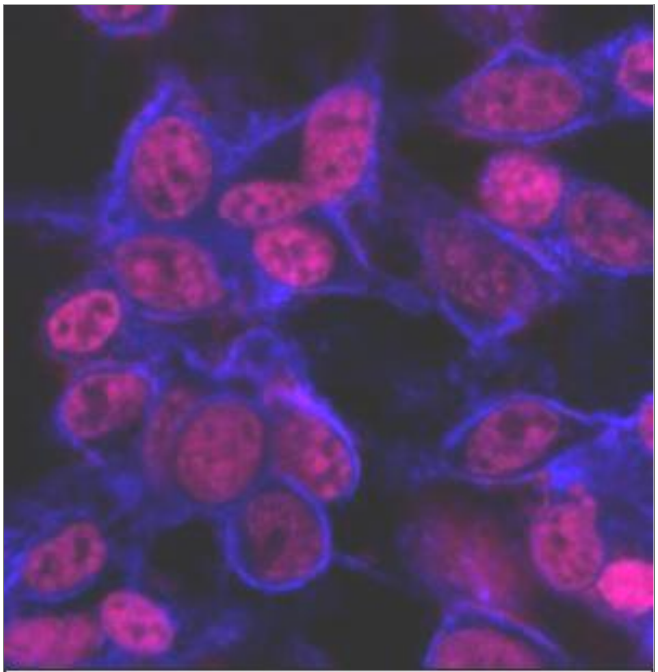
Figure 4 - This image shows that after 24hours, cancer cells have taken up chimeric polypeptide-chemo combination (shown in magenta)

There has also been another recent study (published on December 15th 2010) conducted into the '*Nanoparticle-Based Technologies for Treating and Imaging Brain Tumours*' **[7]**, that was incredibly astonishing, as treating malignant brain tumours is one of the most formidable challenges in oncology. The contemporary brain tumour treatments are hindered greatly by the limited drug delivery across the blood-brain barrier (BBB) to the tumour 'bed'. The researchers specifically used polymer nanoparticles, as they discovered that these nanoparticles could provide prolonged drug delivery directly to the tumour, following direct intracerebral injection; they were able to do so by inducing the nanoparticles to cross the BBB to the tumour, or alternatively by functionalizing the nanoparticles' surfaces with peptides and ligands. This technique allowed the drug-loaded material to be systemically administered whilst solely targeting the cancerous cells or tumour endothelium. These nanoparticles also demonstrated the potential to execute a significant role in the diagnosis and imaging of brain tumours through revolutionizing both preoperative and intraoperative brain tumour delineation, which would result in early detection of pre-cancerous cells, and provide real-time, non-invasive monitoring of the effects of the ongoing treatment.

Taking both of these recent studies into consideration, it is evident that key advancements in nanotechnology have already occurred and will in all likelihood result in a significant change in contemporary cancer treatment; nanoparticle vectors have been proven to be more efficient than their viral alternatives, and unlike any other cancer-combatant these nanoparticles can aid the diagnosis, location and treatment of cancerous cells.

Although the continual adaptation of current research into clinical practice will depend on solving challenges in relation to the pharmacology of nanoparticles, it is already widely conceptualized that these novel nanotechnological treatments will one day enable everyday doctors to target tumours and introduce multiple, pharmaceutically relevant entities for simultaneous targeting, imaging, and therapy through exclusive and (so far) unprecedented techniques.

I personally have formulated my own predictions concerning the future developments of nanotechnology, by acquiring inspiration from my own research and recent successful investigations. Firstly, the day may arise when permanent cantilevers are being injected into the bloodstreams of people most at risk of cancer i.e. citizens with a family history of cancer, smokers etc. as this would allow for the immediate detection of any cancerous cells, thus enabling it to be far easier to treat; as a consequence, cancerous cells and the 'beginnings' of tumours could one day been seen as trivial as the common cold!

Secondly, I have considered the possibility of highly efficient nanowire sensors being developed that can recognise all types of cancerous cells; at the moment it is only breast and prostate (as aforementioned in the introduction). The nanowire sensors’ exceptional accuracy and sensitivity, guarantees its future potential of diagnosing the exact type and stage of cancer existing at a speed that is not currently available to clinicians.

Thirdly, I believe it to be increasingly probable that the conventional methods of chemotherapy will ultimately be replaced with nano-medicine, as there are a great deal of adverse side-effects involved with chemotherapy treatment, such as alopecia, nausea and the constant fatigue. Furthermore, nanotechnology methods of drug delivery have become increasingly attractive to researchers because of their ability to efficiently 'invade' tumours without harming the surrounding unimpaired cells; the blood vessels supplying the tumours are generally more porous than normal vessels, thus when the full-size chemotherapy drugs are administered, there is a high chance of the drugs affecting the surrounding cells as well. However, nanoparticles have been proven to be more efficient at entering and accumulating within the tumour cells, subsequently higher doses of the drugs can be delivered, increasing its cancer-killing abilities whilst decreasing the side effects associated with systematic chemotherapy. In 2009, bioengineers at Duke University developed a simple and inexpensive method for loading cancer drugs into nanoparticles and demonstrated in animal models that this nanoformulation of chemotherapy could eliminate tumours after a single treatment and after exposing the tumour to the drug, the nanoparticles break down into harmless by-products, markedly decreasing the toxicity for the recipient.

With every new innovative advancement in science, one must always consider the risks and ethics surrounding such developments, and there are certainly rather significant ones circumventing the potential of nanotechnological cancer treatments.

Currently, various universities and conglomerates across the world are meticulously studying how atoms interconnect to form larger structures and are continuously learning about how quantum mechanics impact substances at the nanoscale. Elements at the nanoscale behave differently than they do in their bulk form, so understandably, there is a concern that some nanoparticles could be toxic as their possible adverse effects cannot be derived until they are tested! Some doctors are afraid that the nanoparticles employed are so small, that they could easily cross the blood-brain barrier, a membrane that protects the brain from harmful chemicals in the bloodstream (see Figure 5). Additionally, evidence has been found concerning the safety of nanotechnology as, in June 2009, a certain type of nanoparticle had been identified that could cause lung cancer! The particles involved in the investigation were found to induce lung damage by triggering autophagic cell death, and although scientists are now working on drug inhibitors to prevent this from happening again, there is now a great deal of fear and speculation surrounding nanoparticle treatments.

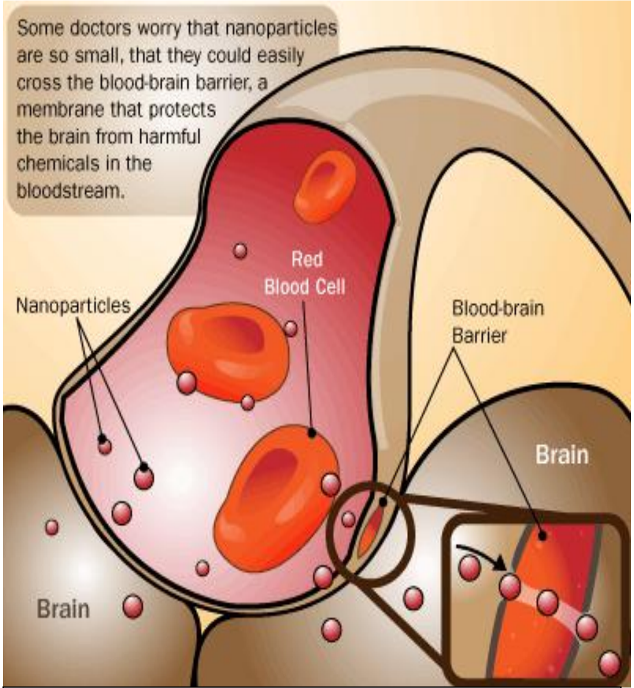

Figure 5 – Nanoparticles and the Blood-Brain Barrier

Furthermore, the general public may be extremely wary of the concept of injecting nanoscale 'machines' into our bodies as there would be paranoia that these 'machines' could lead to undetectable surveillance, thus jeopardising people's right to privacy.

There is also the horrifying speculation concerning the 'transhuman' theory; if nanotechnology became a prominent aspect within medicine, would it allow us to be able to enhance ourselves physically> In theory, medical nanotechnology could make us more intelligent, endurable and give us incredible abilities ranging from rapid healing to night vision. People also fear that if nanotechnology did become capable of this, would this mean two diverse races of the human species could be indirectly created; since almost every technology starts off as very expensive, this would result in a wealthy race of modified humans versus a poorer population of unaltered people? Even Eric Drexler, one of the men who introduced the word nanotechnology, presented a frightening apocalyptic vision of self-replicating nanorobots malfunctioning, and subsequently duplicating themselves a trillion times over, enabling them to rapidly consume the entire world as they 'pull' carbon from the environment to build more and more of themselves. This terrifying prediction is called the "grey goo" scenario, where a synthesised nano-size device replaces all organic material and several organizations are urging nano-scientists to consider these implications now, before it ‘becomes too late’.

Nonetheless, many experts think that concerns like 'grey goo' and 'transhumans' are at best ill-considered and premature, as well as probably unnecessary. Even so, it is evident that nanotechnology will definitely continue to impact on us and incite a great deal of speculation as it continues to develop.

Conclusion

Conclusively, my investigation has demonstrated that nanotechnology definitely has the potential to be the future and sole cure for cancer, as it has already proved itself through various instances to be the most effective and optimum form of future treatment and diagnosis of cancer.

Not only have nanowires and cantilevers been proven for their capability to provide an efficient method of recognising cancer biomarkers in the blood for different cancers, nanoparticle composites have also been developed with opposing properties allowing for more accurate diagnosis and location of cancer (and nanoshells been proven to be more effective cancer gene therapy vectors than the conventional viral vectors.) Furthermore, nanoshells most definitely have the impressive potential to treat malignant brain tumours, due to their effectiveness at delivering the drugs across the blood-brain-barrier, which was previously one of the most challenging aspects of cancer treatment.

There are of course relatively successful methods of cancer treatment already available, such as radiotherapy and chemotherapy; according to the NHS, radiotherapy *‘is used to treat about 40% of people with cancer’***[8].** Nonetheless, both alternative treatments have their own significant risks. For radiotherapy, the proper dosage needed to cure all malignant brain tumours is approximately 12,000 Rads, but such a high dosage is also extremely neurotoxic and deadly, and chemotherapy has an imposing number of risks from alopecia to severe fatigue to ototoxicity to neutropenia (this can leave the patient highly susceptible to infections) to thrombocytopenia (which can result in blood clotting problems).

However, this dissertation has also shown me that more research needs to be conducted surrounding prospective treatment of cancer with nanotechnology, if nanotechnological cancer treatment is to become commonplace. This is because of the number of potential risks and ethical issues surrounding the utilization of nanotechnology in medicine; for instance in June 2009, a certain type of nanoparticle had been identified that could cause lung cancer, rather than cure it!

I deduce that it would be best to focus on the potential employment of nanoparticles and nanocomposites for cancer treatment if nanotechnological cancer treatment is to become commonplace in hospitals by 2020! These developments have already proven themselves to be effective methods of cancer treatment but further research and more clinical trials will need to be conducted in order to ensure the safety of implementing such devices to treat cancer.

This dissertation has also enlightened me to the fact that the developments in nanoshells and cantilevers present an exciting form of cancer diagnosis and could quite possibly provide the answer to what actually causes cancer if detected immediately; perhaps there is a carcinogen that no one has yet considered or detected? I truly believe that it is quintessential that scientists have the freedom to research, study and implement such treatments in the near future as it would prove to be immensely beneficial worldwide.

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