Nanotechnology in Cancer Treatment

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Abstract

Generally, nanotechnology is referred to as the study of manipulating matter on an atomic and molecular scale, smaller than 100 nanometres. Nanotechnology is a fairly recent development and medical applications of nanotechnology, often abbreviated to nanomedicine, have seen large breakthroughs in the last few decades. These breakthroughs include new methods of targeting tumour cells, drug delivery, medical imaging and diagnostic sensors.

Analysis of the prospective uses of nanotechnology in cancer treatment indicates that it could potentially increase the success of cancer detection and destruction, whilst also improving the method and process of doing so.

Introduction

Cancer treatment is one of the most interesting and topical advances in nanotechnology, because it has potential to greatly improve oncology treatment, which is vital as cancer currently kills one in four people.

Cancer (*Malignant Neoplasm)* is a class of disease where cells undergo uncontrollable division. Environmental factors, such as diet and lifestyle, count for 90-95% of cancer cases and hereditary factors count for just 5-10% of cancer cases worldwide. Cancer is a very serious problem to society in this day and age and is currently costing the NHS £5.86 billion each year.

Cancer is classified into different groups depending on the type of cell that hosts the origin of the tumour, these classifications are listed below:

- **Carcinoma** – This is a malignant growth and develops when the epithelial cells mutate. Carcinomas include cancers of the stomach, lungs and skin. These cancerous cells usually spread by a process called metastasis and its Material Safety Data Sheet (MSDS) shows it as being caused by long term (chronic) exposure to a carcinogen. Carcinogenic compounds are most well known as being in cigarettes and this is why smoking accounts for 25-30% of all cancer cases.
- **Lymphoma** – This is a cancer found in the lymphatic cells. The lymphatic cells are cells involved in the lymphatic system which carries 'lymph', a fluid that contains B and T lymphocytes, a type of white blood cell, around the body as part of the immune system. Age, exposure to toxic chemicals, infections and diseases that compromise the effectiveness of the immune system are all linked to increased risk of developing a lymphoma.
  Lymphomas can be separated into the categories of Hodgkin's (HL) and non-Hodgkin's lymphomas (NHL). These lymphomas are very similar except that they are clearly distinguishable under microscopic examination. HL develop from abnormal B lymphocyte cells and NHL's can develop from either abnormal B or T lymphocytes and can be identified by unique genetic markers. There is a good five year survival rate after treatment for HL's, more than 90% for children and 80% for adults. However, the NHL survival rate is lower at 63% for adults but is the same as HL's at 90% for children.

- **Sarcoma** – This is a rare malignant growth of the connective tissue and the bones. Sarcomas are fairly rare and only account for 1% of all malignancies. Due to their rarity, the cases of sarcomas vary significantly, however most cases are commonly treated with surgery, radiotherapy or chemotherapy. The most common type of sarcoma is Gastrointestinal Stromal Tumour (GIST) and accounts for approximately 20% of all sarcoma cases.
- **Germ Cell Tumour** – This is a tumour normally found in the ovaries and the testis, which can be cancerous or non-cancerous. A 'germ cell' is a gamete; an egg or a sperm cell, and in females germ cell tumours account for 30% of ovarian cancer. They can also be found within the cranium, stomach, pelvis, mouth neck and mediastinum, the area in the centre of the chest between the lungs; the mediastinum is the most common place for an EGGCT to occur. However, these tumours; extragonadal germ cell tumours (EGGCT) are very rare. It has been suggested that the occurrence of EGGCT's is a consequence of germ cells being misplaced during embryogenesis. Germ cell tumours can be divided into two broad categories- germinomatous and non-germinomatous. Non-germinomatous tumours usually grow faster, can be diagnosed earlier and have a lower 5 year survival rate.
- **Blastoma** – This is a malignant growth in precursor cells (partially differentiated stem cells). There is a wide variety of symptoms depending on the location of the blastoma, but most symptoms include lumps and swelling in the affected area. Blastomas are most commonly found in children due to the nature in which they form; however a select few cases do involve adults.

Cancer can spread through several different methods, one being through direct contact with nearby organs and tissues.

Cancer can also spread through a process called metastasis, (Figure 1 shows the most common places for metastasis to occur. The brain, the liver, the lungs, the lymph nodes, and the bones) which makes use of the bloodstream or the lymphatic system, allowing the malignant cells to be transported to other various locations within the body in order to form a secondary tumour. If the malignant cancer cells are spread through the lymphatic system then they usually form secondary tumours in the Lymph Nodes.

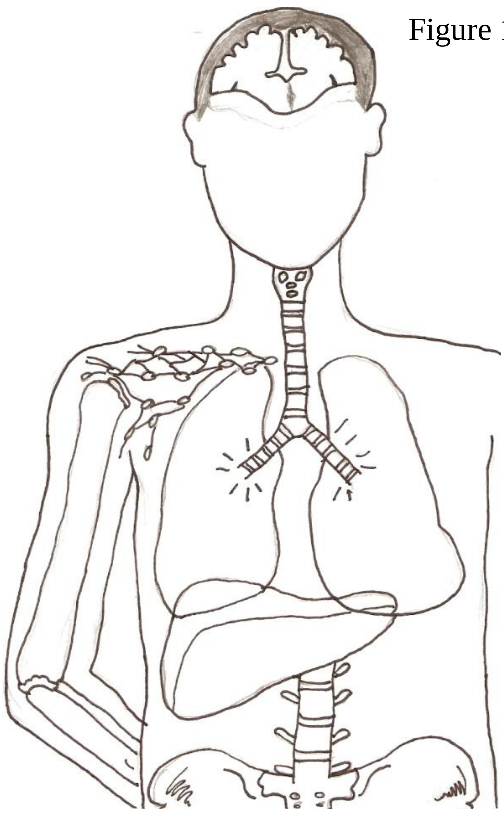


Figure 1

<u>Current Cancer Detection</u>

Present cancer detection methods most commonly include blood tests, magnetic resonance imaging (MRI scans), computerised tomography (CT scans), and endoscopy.

Blood tests involve measuring levels of the different components of blood such a white blood cells, proteins and electrolytes in order to detect diseases, blood cancers and immune system disorders. Typically, an abnormal number of white blood cells suggest there is an infection, as white blood cells fight disease and high levels occur frequently when an individual is unwell.

MRI scans use radio waves to produce cross sectional images of the internal body structure, so that tumours and abnormalities can be identified and analysed. They are particularly effective in detecting brain tumours, primary bone tumours, soft tissue sarcomas and tumours affecting the spinal cord, and they can be used for most areas of the body with varying effectiveness depending on the type of tissue. However, the radio waves can heat the body to a dangerous temperature, whilst the magnetic field has the potential to cause trauma if any metallic foreign bodies are present.

CT scans use X-rays to produce cross sectional images of the body tissues of a similar resolution to MRI scans. They are particularly effective at detecting lymphomas and blastomas. These images can then be analysed by a specialist in radiology who will be able to notice any unusual growths inside the body. CT scans allow malignant growths to be seen without the need for surgery.

An endoscopy can be used to confirm a diagnosis, and involves inserting a long flexible tube with fibre optics to view the surface of an organ or tissue such as the lungs, to ascertain where a tumour is and the extent of its growth. This allows doctors to decide on the most appropriate and best course of action.

Current Drug Delivery

Because cancerous cell are very genetically similar to healthy body cells, it is currently nearly impossible to avoid damaging healthy cells when cancer drugs are used. For example, a side effect of chemotherapy is hair loss which is caused because the hair follicles divide at similar rates to cancerous cells and the chemotherapy drugs attack the hair follicles.

Scientists are hoping that nanotechnology will provide new breakthroughs in drug delivery, in particular bioavailability, because this will be able to reduce, if not prevent, the cancer drugs damaging healthy cells. Bioavailability refers to the degree to which drugs are transported to the areas that they are required and nowhere else, hence in this case, reducing the amount of damage to the healthy cells.

Current Cancer Treatments

Current cancer treatments include surgery, chemotherapy (chemo), radiation therapy (radiotherapy), hormone therapy and immunotherapy. Surgery is one of the oldest and most common forms of treatment and approximately 60% of cancer patients will undergo surgery. If the cancer is diagnosed before it has a chance to spread, then surgery can be an effective way of removing the whole tumour. On the other hand, if the cancer has metastasized, surgery is not used alone, but is often combined with chemo or radiotherapy.

In addition, small scale surgery is used to initially diagnose cancers by removing a section of the tumour for analysis. This is called a biopsy and can also be used to identify the nature of the cancer and whether it has spread.
Chemotherapy uses drugs that can destroy cancer cells. It is an effective method of fighting cancers that have spread to other parts of the body and cannot be treated by any other method currently available. There are numerous drugs that can be used for

chemo and they are individually chosen for each patient based on the grade and stage of the cancer. Two or more drugs can be used together in combination chemotherapy. Chemo can be used to reduce the size of a tumour before surgery and it can also be used afterwards to kill any remaining cancer cells near the removed tumour site or any cancer cells that have spread to other parts if the body. Side effects of chemotherapy include: nausea, hair loss, and vomiting and death of healthy cells. However, anti-sickness drugs can help improve these side effects and side effects normally subside once treatment is finished.

Radiation therapy is when the specific parts of the body containing the cancerous tumours are exposed to a direct stream of radiation in order to kill the reproducing cells. Unfortunately, the radiation will also kill normal cells and due to the damage done to healthy cells; doctors have to be careful with the dosage and timings of the treatment to allow healthy cells to recover. Unlike surgery, it can be used to treat solid and non-solid growths. Like chemo, radiotherapy can also be used to reduce the tumour size before surgery and it can also be used to prevent regrowth after an operation as well as killing remaining cancerous cells. Side effects of radiotherapy are fatigue, dry and peeling skin, nausea and vomiting.

Hormone therapy is a more recent type of cancer treatment that involves manipulating hormones which are normally produced by glands in our bodies. Hormones are used to control growth and activity of certain cells and organs within the body. So, cancer treatment specifically uses the sex hormones produced within our bodies or prevents them reaching the cancer or being made at all with drugs. Hormone therapy does not work for all cancers but can be used on 'hormone sensitive' or 'hormone dependent' tumours such as breast and prostate cancer. Side effects of hormone therapy include, fatigue, muscle and bone pain, digestive system problems and weakness.

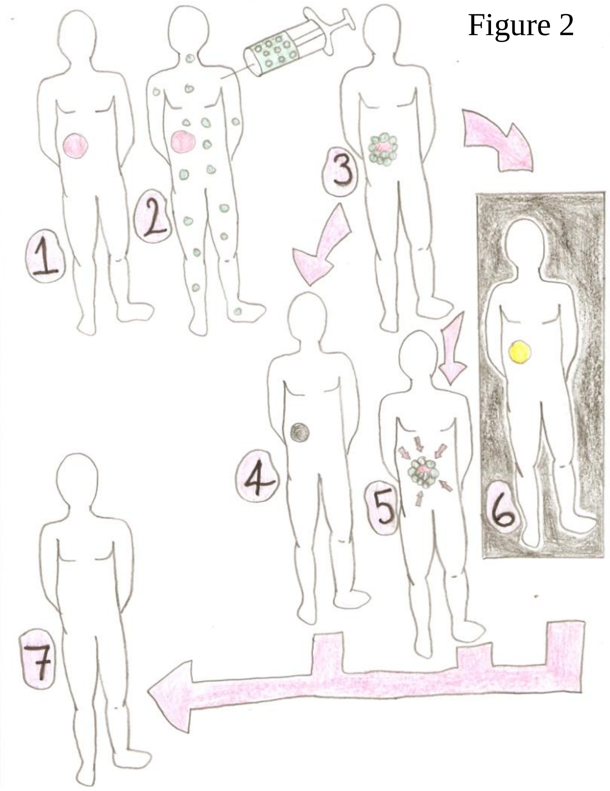
Immunotherapy is also a more recently developed cancer treatment and is based on the body's natural defence system, the immune system. It manipulates bodily functions with medication designed to stimulate the body's immune system to fight cancerous cells by suppressing, enhancing or inducing an immune response. Side effects of immunotherapy are flu-like symptoms, a reaction to the injection site, a rash, reduced blood pressure and difficulty breathing

Discussion

1. Diagnosed Cancer
2. Targeting medication
3. Homing on tumour
4. Killing cancer cells
5. Localised therapy
6. Improved imaging
7. Patient is cured

Figure 2 illustrates the possible ways that nanotechnology could be used to improve cancer treatment and is based on an image from http://en.wikipedia.org/wiki/Nanomedicine It shows seven outlines of human bodies,

Figure 2



representing various stages and types of possible treatments. The first body outline shows cancer as a red circle, the body that follows shows how nanomolecular targeting-medication could be injected, which, as shown on body number 3, would then home in on the cancer. Bodies 4-6 show how the nanoparticles concentrated around the cancerous tumour could be used. Body 4 shows how nanotechnology could be used to kill the cancer; body 5 depicts how localised therapy can target the cancer surrounded by nanoparticles and 6 shows that the nanoparticles could be used to make the cancer appear more obviously on scans. Body 7 is showing a patient cleared of all cancer, suggesting that the possibilities for future nanotechnology treatment within cancer will be able to help cure it.

Nanobots

The word "nano" is actually a length of measurement equal to 0.000000001, therefore nanotechnology must take place on an equally small scale, which is why specialised machines called 'Nanobots' need to be used. Nanotechnology works on a molecular level, constructing and manipulating atoms and the nanobots are essential to enable this new technology to be carried out.

The scanning probe microscope (SPM) is a tool used to move molecules and atoms around. Two early examples of this microscope are the Atomic Force Microscope (AFM) and the Scanning Tunnelling Microscope (STM). As of yet, this tool can only function on a two-dimensional scale, moving atoms from side to side and nanoparticles can also be cut into slices and arranged in this manner. Circuits are then cut into these layers using acids, lasers or ultraviolet radiation.

Potential Cancer Detection

Some cancer cells contain a protein called Epidermal Growth Factor receptor, which can be detected using gold nanoparticles, because the nanoparticles attach themselves to the protein. Research undertaken by Mostafa El-Sayad et al demonstrated that a solution of nanoparticles added to healthy cells and cancerous cells could be differentiated by observing the specimens under a microscope. The healthy cells are not particularly visible as they do not bind to the nanoparticles; however the cancer cells emit a well-defined glow. The use of gold nanoparticles could be particularly beneficial, as they are not toxic to healthy human cells unlike chemotherapy, they are relatively inexpensive, and it can immediately be discovered whether a person has cancer or not: thus allowing treatment to begin without delay.

Like the use of gold nanoparticles, quantum dots can also be used for the detection of cancer cells. A quantum dot is a particle of matter that can have its properties dramatically changed by the addition or removal of one electron. They typically have dimensions measured in nanometres, where one nanometre is 10^{-9} metre or a millionth of a millimetre." Quantum dots use nanoparticles of cadmium selenide; these are injected into cancer tumours, and because they glow when exposed to ultraviolet light, it enables surgeons to remove tumours more accurately.

In parallel to increasing the efficiency of cancer detection, a way of making the detection easier during MRI scans and biopsies is the usage of magnetic iron oxide nanoparticles encased in biocompatible materials. The particles seek out and attach themselves to the tumour cells, magnetising them which either enhances the visibility of the cells in an MRI scan or attracts the tip of the biopsy needle towards the cluster of cells. “Researchers in the Netherlands and Boston, Massachusetts, recently reported in the New England Journal of Medicine that an MRI contrast agent consisting of highly lymphotropic iron oxide nanoparticles enabled clinicians to detect small nodal metastases that otherwise would have gone undetected in 33 of the 80 patients with prostate cancer.”

Drug Delivery

The abnormal properties of nanoparticles make them very well suited to drug delivery. The most promising aspect of the use of nanoparticles in drug delivery is their size because they are small enough to diffuse straight into the cells. This means that the appropriate medication can be inserted directly into the cell’s cytoplasm which not only reduces the amount of damage done to healthy cells but also reduces the time taken for the malignant cells to be destroyed.

The anti-cancer drugs can be encased in polymers which have two ends, one being hydrophilic and the other being hydrophobic – similar to those in a phospholipid bilayer. Once it has been encased, the outer surface can be surface modified by cancer targeting ligands, such as antibodies which allow the nanoparticles to bind only to the cancerous cells and no healthy cells. Once the nanoparticles have bound to the cancer cells receptor-mediated endocytosis (RME) can occur, where the nanoparticles are ingested by the cell and the anti-cancer drugs are released into the cancer cell ultimately killing it.

Potential Cancer Destruction

Currently, the way of destroying cancer cells is painful, isn’t 100% successful, and takes place over an elongated period of time. It also diminishes the patient’s immune system, along with their physical and emotional strength. Nanomedicine aims to better the method of destroying cancer cells by reducing pain and stress to the patients, increasing precision in removal and destruction of tumours, and decreasing treatment time.

Similar to the process of detection, gold nanoparticles can also be used in destroying cancer cells. They can carry chemicals that will potentially destroy cancer cells or they can be used with radiotherapy. Chemical carrying nanoparticles can carry anti mitotic chemicals such as Docetaxel; which interferes or prevents cell division, or chemicals that help stop the tumour cell’s internal defences and decrease resistance such as polyethylene glycol molecules.

During radiotherapy the gold nanoparticles are heated up by radio frequency, which respectively heat the cancer cells and ultimately destroy them. Because the gold nanoparticles do not attach to healthy cells, the radio waves do not harm healthy cells. "In the studies that were initially reported--and this has been repeated now more than 20 times in at least three different animal models--we have seen essentially 100 percent tumour remission."

A development from these ideas is the ‘smart bomb’, which is a nanocell containing a dose of anti-cancer toxin, which can enter the tumour and ‘deploy’ the necessary drugs. The drugs are only released when they enter the tumour, as the outer membrane of the nanocell disintegrates once inside the tumour. One drug used is

typically an anti-angiogenic drug, which prevents the growth of new blood vessels and results in the blood vessels supplying the tumour collapsing.
However a disadvantage with using nanoparticles in cancer treatment is that it could potentially create more cancerous cells, as nanoparticles are able to penetrate cell membranes and defences, consequently interfering with normal cell processes.

Problems

One main concern with the application of nanotechnology to cancer is its danger to human health, as adjusting and manipulating matter on a particular level could create a larger impact on a molecular level. For example, although iron may be relatively harmless in its natural state, it may become a more active element in nanometre dimensions. As nanoparticles are significantly smaller than average particles and consequently act and respond differently to regular particles. This could also present the possibility of many risks, especially where the human body is involved.

Research from Konkuk University, suggests that cultivating plants with nanoparticulate copper has a negative effect on its growth and seedling. The nanoparticles caused a toxic effect and inhibited the plants growth. Similarly, research from the Chinese Academy of Sciences found that nanoparticles of copper caused neurological changes such a transformation in behaviour, morphological changes such as the size and colour of kidneys and biochemical changes such as the components that make up blood in mice, although micro copper had little effect in comparison.

Although plants, mice and humans are not the same species, it is evident that nanoparticles have a relatively toxic effect, and therefore there is a possibility of danger to human health. However, for further exploration to occur, human trials will have to commence, and this in itself causes another problem. It would be unethical to test on humans, but until it is done, it will prevent the use of nanoparticles in pharmaceutics.

This leads to another problem; cost. Cancer is the third largest disease programme in the NHS and cost £5.86 billion in 2009/2010 on the rise from in £3.39 billion in 2003/2004 in England alone. However, the EU funding towards developments in nanotechnology is not solely for nanomedicine, it is spread over several categories, including: nanoscience, technology development, impact assessment and societal issues, nanomaterials, nanomedicine and nanoelectronics. This means that nanotechnology as a whole will advance forwards, but potentially nanomedicine will be limited to the amount of financial support it obtains.

Conclusion

It is undeniable that nanomedicine has huge potential to revolutionise the treatment of cancer. There are numerous initiatives in the midst of taking form, and it is merely a matter of appropriate technology and methods arising for the ideas to become reality. Better cancer detection using quantum dots, enhanced targeting using gold nanoparticles, and more efficient destruction using nanocells are only a few of the future proposals. Once sufficient investigation into the safety of nanoparticles has been undertaken, it is highly likely that the application of nanotechnology in cancer treatment will create a more efficient procedure that will significantly reduce the amount of suffering and concern caused to patients worldwide.

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