NANOTECHNOLOGY AND ITS FUTURE USES IN MEDICINE AND THE DIAGNOSIS, DETECTION AND TREATMENT OF CANCER.

BY
HANNAH PENDLETON
CHLOE OAKES

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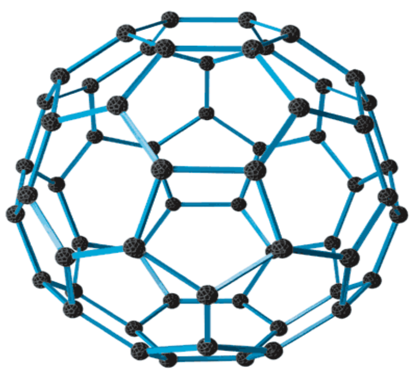
ABSTRACT:

Nanotechnology in the fighting of cancer is an exciting new prospect in medicine and we decided to use our paper to explore some of the concepts. We are interested in the idea that; using nanoparticles, chemotherapeutic agents can be delivered into malignant cells whilst not harming healthy cells, reducing and in some cases eliminating the harsh side effects; such as nausea, hair loss and fatigue, of some kinds of cancer treatment. This can be done by using structures such as 'buckyballs'. Nanotechnology is the study of material that are 10^{-9} of a meter, whilst most cells in the body are around 10^{-6} so because nanoparticles are so small they can be precise where they release the drug.

INTRODUCTION:

In 1985, the allotrope of carbon, fullerene was discovered. The first (and most abundant in terms of natural occurrence) molecule of fullerene discovered was Buckminsterfullerene, a spherical arrangement of 60 carbon atoms. Fullerene is essential in nanotechnology for the production of 'buckyballs'. Buckyballs (Figure 1) led to the development of a certain type of carbon nanotube by Sumio Iijima in Japan in 1991.

Figure 1



Nanoparticles occur naturally in volcanic ash, sea spray, smoke and soot. Nanotechnology is defined as 3dimensional (3D) structural control of materials, processes and devices at the atomic scale and is considered to be one of the building blocks of the 20th century. Nanoparticles posses some remarkable properties; they are 1/6th of the mass of steel and 100 times stronger, very efficient conductors - conducting electricity more effectively than copper and transmitting heat more effectively than diamond. They are also so minute that they are able to enter cell membranes without being averted by cellular defence, however still large enough to interfere with cellular processes to alter the functioning of the cell.

Nanoparticles are already a large aspect of medicine, some of their uses being appetite control, a drug called Megace (Megestrol Acetate) is used to stimulate an appetite in the very weak and ill and people with eating disorders. The drug

contains a synthetic version of the female hormone oestrogen and small particles of this are produced by the ‘wet milling technique’ to stimulate appetite.
Nanoscaffolds are used to regrow tissue and bones – Orthovita is a drug used to repair bone defects by enhancing reabsorption and new bone growth and is used currently in many spine fusion operations. Oestrogen is a large component of nanotechnology, because it is also present in Estrasorb, a hormone therapy lotion containing oestrogen that moderates hot flushes of the skin.
Nanochip technology provides an open platform to run common and customised assays easily. By applying a positive electric current to test sites, it allows rapid movement of negatively charged DNA and RNA molecules.
Rapamine, the immunosuppressant is also a nanotechnology based drug which reduces the effects of organ rejection after an organ transplant. This is only used in patients over 13 years old, due to some evidence that certain nanoparticles are toxic, largely due to their massive surface area to volume ratio.
Nanoparticles are not only used in drugs, but are also used in medical tools, such as TiMESH, a surgical mesh with a titanized surface for high levels of body and biocompatibility is used in laparoscopic surgery to combat hernias, restoring urinary continence, restoration of defected pelvic floors and is commonly used as soft tissue reinforcement implants. It is so effective due to its light weight, remarkable stability and excellent biocompatibility.

Nanotechnology is also currently used in the treatment of cancer. Abraxane is used to treat advanced breast cancer, and is a combination of chemotherapeutic drugs and an aluminium bound form of paclitaxel with a mean particle size of approximately 130nm. This means it is small enough to use the body’s albumin to deliver the chemotherapy. As it does not contain chemical solvents, there is no need for steroids or antihistamines for hypersensitivity reactions beforehand, making it more cost and time efficient. Doxil, an anthracycline antibiotic is used to treat refractory ovarian caner, haematological malignancies and an AIDS related cancer called Kaposi’s sarcoma (a tumour of the connective tissue). It works by intercalating the DNA of cancerous cells. Doxil is composed of lipid nanoparticles with a polyethylene glycol coating, which reduces the risk of potential impact on the immune system. However the use of Doxil may lead to life threatening cardiac toxicity, leading to congestive heart failure.

Also proving to be an impressive help in regards to current treatments of cancer are liposomes. Liposomes are man made vesicles made of a lipid bilayer and are commonly used nanoparticles for the delivery of specially targeted drugs, as well as vaccines into the body. Liposomes have a natural ability to target cancer. Healthy human blood vessel endothelial walls are surrounded by endothelial cells bound together by tight junctions. Tumor cells do not have the same level of intercellular seal and are said to be ‘leaky’ – i.e. the Enhanced Permeability and Retention effect. Liposomes less than 200nm carrying therapeutic drugs such as Doxorubicin and Daunorubicin (Doxil and Daunoxome – both chemotherapeutic drugs) and Camptothecin (a DNA enzyme inhibitor) can enter the tumor.

Nanoparticles are so small they can penetrate cell membranes whilst avoiding their defence systems, yet are large enough to interfere with cellular processes. The use of nanoparticles combines with siRNA (a double stranded molecule of RNA that is up to 25 nucleotides in length) as a delivery system, prevents the RNA molecule from being destroyed by the body before reaching the cancerous cell target. This is already being used in the treatment of Ewing's Sarcoma (a rare cancer of the bone and soft tissue). The siRNA molecules alter growth-promoting genes in the DNA of sarcoma molecules. Recent drug tests saw mice grafted with human tumors, and the use of the nanoparticle / siRNA delivery system was shown to reduce cancerous cell replication by up to 80%.

Nanoparticles are not only used in the direct treatment of cancer, but for controlling the negative side effects of vigorous cancer treatment like chemotherapy. For example EMEND is used as anti-nausea treatment for patients undergoing chemotherapy. Most chemotherapy-induced drugs stop nausea and vomiting by blocking the stomachs signals, but as chemotheraphy can affect the stomach and the brain, patients still feel or are sick. EMEND contains precipitant formulated NanoCrystal drug particles to stop the brains signals. It contains aprepitant, a type of neurokinin receptor antagonist. Aprepitant works by blocking q receptor in the brain called naurokinkin-1 which triggers chemotheraphy related nausea and vomiting, so that a certain nausea inducing proteins cannot bind with the receptor, preventing nausea and vomiting.

Nanotechnology has other uses. There is current research focusing on macromolecules during the earlier stages of cancer progression. It provides rapid and sensitive detection of cancer related molecules and can detect molecular changes occurring even in the smallest percentage of cells. Currently medical imaging can only detect cancer once it has made a visible change to the tissue and then treatment still has to be assessed by biopsies.

Cancer therapies at present are limited to surgery, radiation and chemotherapy, all of which cause some risk of damage to normal tissues due to the cytotoxic nature of the drugs which can either kill healthy cells or incompletely eradicate the cancer cells. Some of the potential damage it can cause is; nausea, neuropathy, hair- loss, fatigue and compromised immune system.

A positive improvement is that there are nanocarrier based drugs available which rely on passive targeting. Nanoparticles escape through blood vessel wall into tissues (especially leaky blood vessels and defective lymphatic drainage) therefore accumulating in them. This means they concentrate attached cytotoxic drug where needed, therefore protecting healthy tissue.

Furthermore, the Food and Drug Administration (FDA) recently approved Investigational New Drug (IND) applications for nano–formulations, enabling clinical trials for breast, gynaecological, solid tumour, lung cancers, lymphoma, central nervous system and urinary cancer treatments. For example Drs. Caius Radu, Owen Witte and Michael Phelps at the Nanosystems Biology Cancer Centrein California are developing a new kind of PET imaging agents [^{18}F]-FAC, for use in assigning patients with chemotherapeutic drugs like gemcitabinr, cytarabine, fludarabine and others to treat advanced breast cancer, ovarian and pancreatic cancers as well as leukemia and lymphomas. Tumors responsive to these drugs will show up as bright image in PET scans when patients are given [^{18}F]-FAC. These trails have so far only been tested on eight healthy volunteers so are in the early stages of development, but undeniably offer a positive improvement where nanotechnologies are concerned.

DISCUSSION:

Nanotechnology has proved itself to be a medically revolutionary concept, particularly in the areas of cancer treatment. The uses of nanotechnologies in regards to treating cancer are separated into two areas: diagnosis and detection, and screening.

To begin with, diagnosis and detection regarding the uses of nanoparticles has the potential to be transformed. There is a whole range of uses that screening and detection of cancers can be improved, as will be highlighted below.

Primarily, nanotechnology allows screening devices to detect cancerous or pre-cancerous cells. Two fundamentals that are required for this are: something to specifically identify a cancerous cell, and something to enable it to be seen. For example, antibodies to identify specific receptors to be projected onto the surface of cancerous cells, so that they can be coated with nanoparticles such as metal oxides. This then produce a high contrast signal on MRI and CT scans. The metal oxides then bind to the cancerous cells, lighting them up on the scanner. Gold particles can also be used to this effect for endoscopic techniques (for example colonoscopies). This then allows doctors to see cells and molecules that are undetectable through conventional imaging.

In regards to screening for cancer, nanotechnology proves to be very useful.
It can be used for biomarkers in tissues and fluids for diagnosis.
Cancers differ from each other, and so each contains different biomarkers, meaning that identification of cancers may require the detection of numeral biomarkers so that the correct treatment can be administered.
For example, the use of quantum dots – nanoparticles of a semiconductor material, for example selenides or sulfides of metals such as zinc and cadmium, and range from 2-10 nanometres in diameter. The most useful and impressive property they possess in the field of medicine, is that quantum dots emit photons when excited, visible as light to the naked eye.

This could become an essential surgical tool - by injecting cancerous cells with quantum dots, it will become possible to identify cancer and extract in one operation. The wavelength of the photon emissions is dependent on the size of the quantum dot, and it is possible to change the wavelength, therefore changing the colour of the photon emission. Changing the quantum dots' colour of light emission is called the 'size quantisation effect'; the smaller the dot the further it is to the blue end of the visible light spectrum and the larger the dot the further to the red end.

Quantum dots, once manufactured, appear either in solution, or as a powder. Due to minute size, one kilo will provide enough dots to serve on an industrial scale. Technology now has the ability to produce high quality quantum dots on a mass scale.

Not only can they be used in surgery diagnosis, quantum dots could also be used for non-surgical diagnosis by either tuning the photon emission to infra-red or using a detector to map the exact location of the cancer. This provides a way to diagnose skin and ‘surface’ cancers by eye. Using signals from quantum dots coated in antibodies, it is possible to screen for different forms of cancer, thus allowing oncologists to determine if cells are cancerous or healthy by the different colour lights they see. These light emissions are called ‘photoluminescent signals’. (13)

The second area in which cancer treatment is developing thanks to nanotechnology, is the treatment of cancer - eradicating tumours, as well as diagnosing and detecting cancers. There are a number of different ways in which nanotechnology can be used to treat cancer, a number of which will be outlined below.

Primarily, nanotechnology has been used to develop nanoparticles with the aim to act as nanocarriers. Nanocarriers are being used to carry chemotherapeutic drugs, and deliver medication directly to the tumour, hence sparing healthy tissue. Advantages of this process are in abundance – nanocarriers protect drugs from degrading before they reach their targeted molecule, along with enhancing the absorption of drugs to tumours. Nanocarriers also allow a more effective control regarding timing and distribution of drugs to the tissue, alongside preventing interaction with healthy tissue, thus avoiding side effects.

As oppose to passive targeting, (as mentioned previously), active targeting is being used to develop drugs that will target drugs actively to cancerous cells, based on the molecules that are present on the cells surface. Nanoparticles can be attached to molecules that bind particular surface receptors to actively target cells that express certain receptors on molecules. Active targeting can also be used to bring drugs to cancerous cells, by inducing the cell to absorb nanocarriers. To further reduce interaction between healthy tissue and also increased the efficacy of chemotherapy, active targeting can be combined with passive targeting.

Nanoshells are proving to be an encouraging possibility in treating cancer, where a technique has been developed to physically destroy the cancerous cells from within the tumour thermally. They can be designed to absorb light of different frequencies – near infrared light is applied to the cancerous cells, which are absorbed by the nanoshells. This therefore creates an intense heat within the tumours, destroying the tumour cells but not harming surrounding healthy cells. The cancer cells take up the nanoshells via active transport – which involves conjugating peptides or antibodies to the nanoshell surface.
Also conducting research surrounding nanoshells is Professor Jennifer West, of Rice University. Researchers in this department have been developing a new type

of nanoparticle that has optical properties that can be altered and tuned, to absorb or scatter light depending on what is required, because of the transparency of the blood and other body fluids. Also under development under West's eye are: a photothermally modulated drug delivery system, optically controlled valves for microfluidics devices, and also rapid, whole blood immunoassay.

Other studies have demonstrated the possible functions of carbon nanotubes in detecting and destroying aggressive forms of breast cancer. In the body there are genes to help regulate the growth and proliferation of human cells, called HER-2. Breast cancer cells have multiple copies of the gene, which results in an overproduction of the HER-2 enclosed protein, which is associated with the aggressive tumours. Carbon nanotubes being developed to form dual purposed nanostructures, where anti-HER-2 drugs are attached to carbon nanorods, to then thermally destroy the cancerous cells after being subjected to near infrared radiation. Currently the tests have been taken on cell cultures of an antibody raised in chickens, and the results showed nearly a 100% eradication of the cancer. The next step is to test this process of mice, and go from there.

Researchers at MIT and the University of California have been conducting research surrounding the uses of gold particles. The procedure is as follows; Gold nanorods are injected into the bloodstream, and stay in healthy blood vessels but exit leaky blood vessels, therefore accumulating at the site of tumours. A near infrared laser is used to heat the particles, and so heats the whole tumour. The increase in temperature then increases the production of a stress related protein, p32. The amino acid Lyp-1, then binds with the protein, and forms a spherical particle called a liposome. Chemotherapeutic drugs are then delivered to the tumour inside the liposome. When this liposome enters into the bloodstream, the amino acid on the particles are attached to proteins that have been pushed to the surface, therefore allowing more of the drug to be delivered.
Another treatment regarding gold particles is where the gold particles are attached to a tumour-killing agent, called tumour necrosis factor alpha (TNF), as well as a molecule of Thiol-derivatized polyethylene glycol (PEG-THIOL). The PEG-THIOL allows the TNF to hide from the immune system, so it will not be attacked by the body's immune system. This combination of the TNF and PEG-THIOL is also known as Aurmine, and had positive results with phase 1 of clinical trials. Phase two is currently being planned, where Aurmine is to be combined with other chemotherapeutic drugs.
Nanorods have been proved to be more effective than spherical gold nanoparticles, because nanorods can be different lengths, so absorb different frequencies of infrared radiation and more effectively than spherical particles.

Aurolase ® is another treatment in which cancerous cells are destroyed using heat. Current animal studies have show positive results, with no toxicity problems, and initial human pilot studies are currently in progress, looking at the treatment of refractory head and neck cancer.

Aurolase ® has been defined as ‘the particle-based thermal ablation of tumours’, and its trials show that it can ‘treat irregularly shaped tumours with precision’, and it also preserves surrounding healthy tissue and physiological structures.

Additionally working towards the future eradication of cancer is the work of the company Nanobiotix.

Nanobiotix are currently developing an impressive treatment for cancer - NanoXray ™, which is aimed at stopping the causation of damage to healthy cells during screening for cancer, and cancer treatment. An increased dose of a standard x-ray can be achieved by activating a nanoparticle which is situated in the core of the NanoXray ™. The nanoparticle is named nbtxr3, and on its activation, increases the efficiency of standard x-rays, due to the generation of free radicals and heat produced after x-ray absorption. The nbtxr3 particle has been designed with properties to penetrate only tumour cells, and also to exchange normal x-ray radiation into the release of electrons that are responsible for generating free radicals. The sheer minuteness of the particles means there is an improved dispersion and diffusion of the effect in which nbtxr3 has on tumour cells, and the fact that the particles are mainly spherical means that they are able to morph, thus increasing penetration of cells.

Nbtxr3 particles are activated ‘in vivo’, in order to destroy cancer cells upon irradiation. A basic outline of the process is that the free radicals that are generated by the activation of the nanoparticle are very reactive; so react inside the body, causing damage to nucleic acids, proteins, and also membranes – therefore resulting in biological consequences. Ultimately, this means that this reaction will destroy tumour cells and allow high doses of reactive oxygen species (as the free radicals generated are oxygen free radicals) with cytotoxic action within the tumour cells. The benefit of this is that once the nanoparticles have accumulated within the malignant tissue, normal x-ray radiation is applied; (to produce a local therapeutic effect) meaning damage is not caused to normal body cells, because of the differentiation between cancerous tissue and normal body tissue.

Nanobiotix have presented an encouraging start to a process which is currently undergoing preclinical studies. The nbtxr3 particle has a large surface area, a biocompatible coating (to increase stability in physiological fluids) and is an inorganic material, making it inert, and therefore not a drug. This nanoparticle also remains inactive unless it has been activated, meaning it does not have any further effect on the body.

CONCLUSION:

It is undeniable that the development of drugs and treatments involving screening and diagnosis of cancer and cures for cancer is well underway, however it is evident that it is an ongoing process, and much is still to be achieved.
For example, any potential health risks have to be examined in great depth before nanotechnology can be completely verified in its research, treatment and diagnostics surrounding cancer.
The Nanotechnology Characterization Laboratory has to perform a whole range of tests in order to decide of the safety of nanoparticles, and other nanotechnologies. The tests incorporate the evaluation of; effectiveness of nanomaterials, their physical properties, and also their biocompatibility. A common test ran is that of toxicity and safety of nanomaterials, which is undergone in laboratories and on animals.
One of the most prominent problems towards the use of nanotechnology as a medical use of treating cancer is that there is unresolved debate regarding the toxicity of nanoparticles. Although there appears to be nothing specifically toxic about nanoparticles, research has shown an association between toxicity and tissue damage (in tests run on animals) regarding carbon nanotubes. However, this is still to be resolved, and it is not untrue to say that nanoparticles themselves are far less toxic than, for example, chemotherapeutic drugs in which nanoparticles may be carrying if they are acting as nanocarriers.
Furthermore, there is no denying that there are other setbacks in need of a solution regarding nanotechnology. For example; determining the right sized nanoparticles to use, how to hide nanoparticles from the immune system (a specific problem for Aurmine treatment), and choosing the correct targeting molecule to bind to a tumour.
All of the above take time to surmount, but once the creases have been ironed out, and tests and studies have been verified, we have a very bright future concerning the continuous battle against cancer.

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