ADVANCES IN NANOTECHNOLOGY IN THE DETECTION, DIAGNOSIS AND TREATMENT OF CANCER

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PASS WITH MERIT

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ABSTRACT

This paper will discuss the groundbreaking research into the applications of nanotechnology in medical research; in particular, research pertaining to the development of detection, diagnosis and treatment of different cancers in the body. This specific topic is often in the press and is of particular interest in the public arena. Therefore, due to our personal interests into this specific field of nanotechnology medical research, we thought that this would be a collectively suitable topic for us to research and to develop a greater depth of understanding and incite within this discipline of science. We feel that this is an extremely important area of interest as so many lives are needlessly lost each year due to inefficient detection and treatment of cancer. Many of the treatments in current use are very crude and potentially harmful to the patient's general health and wellbeing.

INTRODUCTION

Research into the application of nanotechnology in medicine currently attracts a large proportion of the funding designated for medical research as a whole, and there are many valid and significant reasons for this. A small amount of research will uncover the fact that with nanotechnology you can achieve things that were once only dreamed about and even thought of as being within the realms of science fiction. Nowadays, however, new applications are being developed every year. So what exactly is nanotechnology? It is the manipulation of matter at an atomic or molecular scale. This means that it is possible to produce devices and materials with a size of one hundred nanometres or smaller. That is 1x10^{-3}mm or smaller. Consider that the width of three atoms in line is about 1 nanometre and that the diameter of a human hair is 200 000 nanometres. This means that the devices made are a two thousandth the diameter of a human hair or smaller. However, before we get too enthusiastic about the minuscule scale at which this science is undertaken, we have to consider what advantage it has in relation to medical research. Just what is it exactly that makes being so small advantageous? It is largely on account of the size of cells in the human body. The eukaryotic cells in our body can be as small as 10µm, which is 10 000 nm, and so this means that the nanomolecules produced can be targeted at individual cells which may be infected with some form of disease. This precision allows for prevention of unnecessary damage to otherwise perfectly healthy cells. This, in turn, will prevent or lessen the onset of illness that the patient may suffer as a consequence of the treatment. Well known research, which is utilising this small scale advantage, is progressing into more effective methods of dealing with cancer which will subsequently be discussed as the main topic of this paper. An

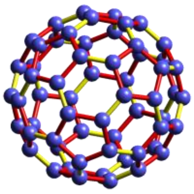


Figure 1 - Buckminsterfullerene

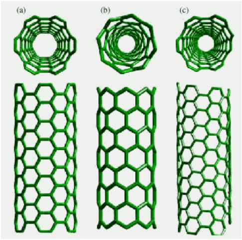
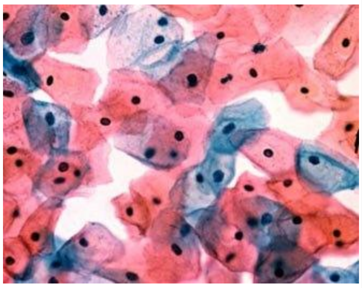


Figure 2 - Nanotubes

Formatted: Font: (Default) Segoe UI, 12 pt example of this is buckminsterfullerene or buckyballs as they are popularly known; C_{60}, in which the atoms are arranged in football like spheres (see figure 1), each carbon forming one double and two single bonds with surrounding carbons. This can then form a cage in which a dose of medicine can be placed and specifically targeted at cells making treatment far more effective. Other uses for this molecule and similar molecules such as nanotubes (see figure 2), which are similar but, surprisingly, have a tube like shape, are currently being researched by many scientists. Harry Kroto and his colleagues received the Nobel Prize for the discovery of buckminsterfullerene, demonstrating the significance of this event.

DISCUSSION

Detection



Around 7.9 million people die from cancer each year. Cancer is a disease which occurs when ordinary cells mutate so that they grow in an unrestrained way. The uncontrolled growth of cells causes a lump called a tumour to develop. If left untreated for a period of time, the tumour can cause serious problems. It can then spread into other healthy tissues nearby which causes strain on other parts of the body. The tumour can also spread to the rest of the body through the blood or the lymphatic system which, in turn, means that the tumour has become malignant.

Although a mass of research has been done, there has been no substantial progress in the past 50 years in the fight against cancer. It is apparent, therefore, that the progress in cancer treatment has been slow but the emergence of nanotechnology brings new hope for significant breakthroughs to be achieved regarding cancer in the near future.

To try and minimise the number of deaths and lessen suffering from cancer by 2015, the National Cancer Institute has focussed its research on mastering the power of nanotechnology in order to substantially change the way we diagnose, image and treat cancer.

The objective of The National Cancer Institute is to prevent and control cancer by developing nanoscale devices capable of distributing cancer preventing agents around the body. Multicomponent Anticancer Vaccines are also being developed using nanoscale transport vehicles. The second aim is the detection of cancer earlier than has been previously possible. This is achievable by creating implantable, biofoulding-indifferent molecular sensors that are able to detect cancer associated biomakers. These are subsequently collected for ex vivo analysis and the results can then be wirelessly transmitted. 'Smart' collection platforms are also being developed for simultaneous mass spectroscopic analysis of multiple cancer-associated markers. Another intention of the NCI is to master the technology of imaging diagnostics.

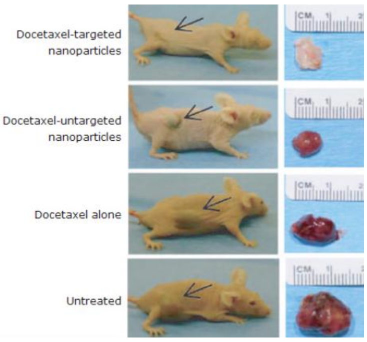
They plan to achieve this by firstly: designing 'smart' injectable, targeted contrast agents that improve the resolution of the cancer to the single cell level. Secondly, by engineering nanoscale devices capable of tackling the evolutionary and biological diversity of the multiplying cancer cells that produce a tumor within an organism. The third goal is the development of multifunctional therapeutics which will progress nanoscale devices that mix diagnostic and theraputic functions. Another important goal is to improve the quality of life the cancer patient suffers due to the inevitable health deteriation that is an unfortunate consequence of the disease. By designing nanoscale mechanism that can deliver medication optimally, symptoms such as, pain, nausea, depression and loss of apetite can be limited. The final aim of the National Cancer Institute is to deliver interdisciplinery training. There is a large emphasis on providing training in molecular biology systems to nanotechnology engineers and nanotechnology training to cancer researchers. In addition, creating an interdisciplinary coursework/degree programme means many new generations can be trained in both cancer biology and nanotechnology which when they work together will be able to make massive progress in the development in this field.

Nanotechnology in Pancreatic Cancer

Pancreatic cancer has a stunningly low survival rate of less than five percent due to the fact that it is usually diagnosed at an advanced stage when the cancer has developed. The primary symptoms, such as pain, jaundice or weight loss, often do not permit the disease to be caught early enough for surgery and chemotherapy to be effective.

Emory researchers have created equipment for earlier detection of pancreatic cancer by attaching a molecule that binds specifically and only to pancreatic cancer cells to minuscule "nanoparticles" made of iron oxide.

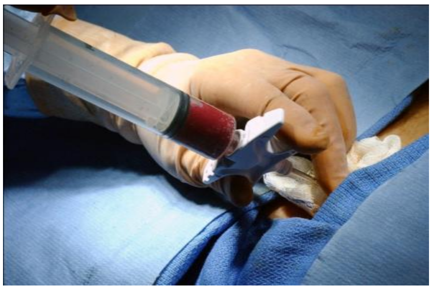
The particles become easily visible under Magnetic Resonance Imaging (MRI) due to the use of the iron oxide. The mechanism was originally tested on mice with implanted human tumours. Because the particles are studded with near-infrared dyes, they can be seen on a scan with a specialised camera. The iron oxide particles have a core, just 10 nanometres in diameter, and a polymer coating. The molecule that allows the particles to distinguish between pancreatic cancer cells and normal, healthy cells is a small engineered protein which binds to the receptor on cancer cells. This protein is based on a natural protein found in humans, urokinase plasminogen activator (uPA).



Urokinase plasminogen activator is useful in discriminating tumour cells from regular pancreas cells irritated by chronic pancreatitis; a challenging task in clinical diagnosis. Because only the cancerous cells have these receptors on the outer surface of their cell surface membrane, particles coated with the uPA are only taken up by the cancer cells and not by normal pancreatic tissues, therefore preventing unnecessary harm to perfectly healthy cells. Tumour endothelial cells lining blood vessels also take up the particles. A low signal can then be detected in the spleen and the liver.

Tumours as tiny as one millimetre across can be detected by MRI or optical imaging. The technology now needs to be refined and perfected so that it is ready to test on humans. Patients that have a higher risk of developing pancreatic cancer, such as those presenting with inherited cancer risk, chronic pancreatitis or new-onset diabetes, could benefit if this method of detection was successful.

Diagnosis



Nanotechnology is coming up with new and refined ways of diagnosing cancer both before and after it has developed into a disease. This research is being carried out on two main fronts: the laboratory-based diagnostics and the in vivo diagnostics.

Traditionally, cancer is suspected based on a person’s symptoms, physical examinations and results from a screening test. However, to diagnose a person with cancer, a diagnostic test has to be performed on the patient. In the case of suspected leukaemia, this is simply done by taking a blood sample, whereas other cancers require a biopsy. The biopsy is obtained by the use of a hollow needle from the area that is suspected to contain the cancerous cells. Practitioners make a successful diagnosis when cancer cells are found on microscopic samples from the biopsy.

Resulting from the advancement of nanotechnology, non invasive methods of diagnosing cancer have been developed. An example of a non-invasive cancer diagnostic method is optical imaging. This enables observation of the distribution and dynamics of proteins, with spatial three dimensional imaging at the nanoscale and with a short time resolution which can be performed in vivo.

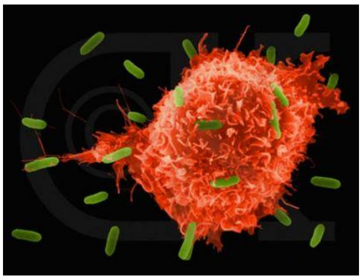
Optical imaging is a clinically safe and relatively inexpensive technique that has the potential for diagnostic cancer imaging and is used in vivo. This technique is a sensitive, non-invasive and a non-ionizing way to carry out in vivo tests without causing any harm to the patient or subject. There are two main components in optical imaging: the optical imaging component and the optical contrast component. The optical imaging component is the system responsible for generating an image of a component surface which emits light that is, partly, radically symmetrical. The optical contrast component is used in biological systems to intensify the contrast enhancing properties. The optical contrast agent has the ability to reduce the background signal and increase the resolution.

There are a few things that should be considered before using or developing optical contrast agents for cancer diagnostics: firstly, the contrast agents with the excitation and emission band maxima are preferred for deep tissue imaging; they should have a high quantum yield for obtaining a strong florescence signal and have a high extinction coefficient for effective absorption. Secondly, they shouldn't have photo synthesizing effects and, thirdly, the photo-stable agents should be hydrophilic. This allows an aqueous based formulation to be made easily and the easy target of cancerous cells. The optical contrast agent has to have appropriate cancer specific delivery systems for targeting the cancerous cells.

There are, however, limitations to the optical contrast agents. For example, the fluorescent optical agents have been widely studied and it has been discovered that organic fluorescent lights get photo bleached really fast. The florescence fades away when exposed to the excitation light source, especially when a laser is used as the source; this limits the sensitive detection of the target. Furthermore, some of the fluorescent compounds have been found to be slightly toxic.

In recent years, optical imaging has used powerful mathematical modelling of light propagation; highly sensitive charged-coupled device (CCD) and laser technology have been used to see through biological systems.

The sensitivity of the optical contrasting agent has lessened the resolution of the image that can be acquired from optical imaging. Optical imaging has been limited to thin tissue because of the low penetration of both the ultraviolet and the visible spectral range of light. To improve the penetration of the light near-infrared light (in the spectral range of 650-900nm) can be used to penetrate even through bone, this is because of the low absorption of tissue components such as water and haemoglobin.



While improving the optical-based imaging systems to help in the diagnosis of cancer, it is important to understand how light will interact with tissue within the body. It can interact with light photons in a number of different ways; for example, the light can be absorbed, dispersed or reflected. It is also helpful to take into account that all biological tissues are slightly 'auto fluorescent' when they are in contact with either visible light or ultraviolent spectrum. The tissue's auto fluorescence originates from natural tissue florescence molecules that should not be mistaken for an optical contracting molecule, which could lead to an incorrect diagnosis. If the near-infrared light is to be used in the optical imaging, it is important to understand how the light photons will interact both with healthy cells and with cancerous cells.

On the whole, optical imaging would be a much better method of diagnostic cancer imaging because it eradicates the problem of acquiring biopsy samples from areas of the body which are difficult to reach. For example, the acquirement of bone marrow in the case of suspected bone marrow cancer or myeloma etc.

There are other methods that can be used to diagnose cancer; one of the methods is to understand the human cells on a nanoscale. This would enable doctors to diagnose cancer with ease. However, the biological field still lacks the tools to carry out cell research at this scale but a combination of biology and nanotechnology will eventually have the potential of providing a comprehensive understanding of a healthy human cell. If this was achieved, then we would be able to understand the function and organisation of cells with specialised mechanics, forms and functions. We would be able to know whether an average cell can defend itself or not and how it behaves when it is in the vicinity of a cancerous cell. If we know how a healthy cell behaves in its natural environment, we can then find out how it will behave around a tumour making the diagnosing of cancer even easier.

Treatment

Currently, all methods for treating cancer are invasive, damaging to the health of the patient and don't always result in successful eradication of the cancer tumours. These current methods are: surgery, radiotherapy and chemotherapy. Due to the invasive nature of these treatments, many cancer patients feel more ill after than they did before the treatment. However, this is where nanotechnology is revolutionary in the treatment of cancer. Because of the nanoscale, it allows individual cells to be targeted, preventing unnecessary damage to healthy tissues as caused in traditional treatments. There is a number of exciting nanotechnology methods in development, earmarked for future use.

Nanocarriers

With conventional chemotherapy the cytotoxic cells not only kill the cancerous cells but healthy ones as well. This then causes unpleasant and sometimes fatal side affects such as nausea, neuropathy, hair-loss, fatigue and compromised immune function. However, nanoparticles such as buckminsterfullerene can be used as carriers for chemotherapeutics to deliver the medication directly to the cancerous cells, therefore not affecting any healthy cells. Advantages of nanoparticles are: they prevent degrading of the drug before it reaches the cancerous cells; they make absorption of drugs into the tumour and cancerous cells much more efficient meaning not as much of the drug will be necessary; they allow more control over the timing and dosage into the cells which then allows oncologists to evaluate how well they work; they prevent the drugs from damaging any surrounding healthy tissue and cells, therefore preventing the many side affects associated with conventional chemotherapy.

Passive Targeting

Nanocarrier drugs which rely on passive targeting use a process known as "enhanced permeability and retention". Due to the nanoscale of the particles, it is possible for them to fit through the gaps between epithelial cells of blood vessels, mainly the capillaries, which facilitate fast and easy access into the different tissues of the body. This effect is intensified in tumours, which tend to have many capillaries and 'leaky' blood vessels along with a defective lymphatic drainage due to the rapid rate that they grow. This causes the nanoparticles to accumulate in the tumour and so concentrates the cytotoxic drug that is attached to the specific area where it is needed. Therefore, healthy cells are further protected.

Active Targeting

One main part of research in this field and one that will hopefully be successful in the near future is 'active targeting'. The nanoparticles will actively target the drugs to the cancerous cells based on the glycoprotein receptors on the outer side of the cell membrane; these act like an identity card for the cell. This can be done by attaching molecules, which bind to the specific receptor of the cancerous cell, to the nanoparticles. The nanoparticles can even induce the cells to absorb the nanocarrier which further targets them. This, teamed with passive targeting, can further increase the efficiency of the chemotherapy and therefore cause a speedier reduction in the size of the tumour. As a result, a smaller dose of the drug is needed and this reduces side effects to a minimum.

Destruction from within

As well as the chemotherapy approach, there is current research which involves the physical destruction of the cells; hence the name ‘destruction from within’. An example is nanoshells which are currently being used in laboratories to thermally destroy tumours from the inside. They are designed to absorb different light intensities and so heat up cells in the process. This is analogous to the natural immune response of the body that causes the development of a fever during illness, also known as hyperthermia. The aim is to raise the temperature to a high enough level to destroy the dangerous cells. However, with nanoshells the heat can be focussed on one area whereas when you develop a fever the whole body heats up which causes the enzymes involved in many metabolic functions to stop working. This is why it is extremely dangerous if the body temperature increases by only a couple of degrees. By focusing the heat on one group of cells you can successfully destroy them without affecting any healthy cells. It is near-infrared light that the nanoshells absorb and within just a few seconds they can be heated to over 70°C. Hundreds of nanoparticles, which are often nanotubules, can fit into one cell. The cancerous cells have receptors coating the outer surface of the cell which normal cells do not have. The most predominant one is the receptor for detecting folate. Therefore, the nanotubules are coated in folate molecules so that they only bind to the receptors on cancerous cells and do not harm any healthy cells. There is current research designed to refine this technique by developing a way to attach antibodies to the nanotubules which can then directly target the antibodies on the surface of the cancerous cells, increasing further the efficiency of the treatment. Another example in development is magnetic nanoparticles which, similar to nanoshells, destroy the tumour by hyperthermia and is also visible through Magnetic Response Imaging (MRI).

CONCLUSION

It is clear that the progression of this research is limited by the current available technology. New ideas are thought of every year but many are not yet possible. The frustrating truth is that the cognitive understanding of nanoscience is developing at a much faster rate than the technology used to create the different nanoparticles. Research into certain theories has to be halted until the technology to continue is available. Much more precise and easily controllable tools are needed to manipulate the nanomolecules in order to create them to a greater complexity.

If the research into the use of antibodies as a treatment advances it will truly revolutionise our perception and attitude to cancer. Survival rates would be dramatically increased and the duration of treatment would be markedly reduced. However, this treatment could be potentially expensive and therefore it would be reliant on whether the government decides to provide extra funding for the NHS to invest in it. Because cancer is caused by mutations of the DNA coding, every episode is different. This means that specific antibodies would need to be produced for each patient and this may prove too problematic and cost prohibitive.

Furthermore, the ethics surrounding the required research in this field must also be considered. Testing must be carried out to determine whether the new treatments will be safe for use on patients and this will involve testing on animals which many people perceive to be cruel and unethical. In addition, the animal's body systems and cells may react differently to that in humans and so the testing is not 100% trustworthy. Some testing therefore would need to be carried out on people to fully discover the effect of the drugs. This creates a problem as it needs to be tested on a person who already has cancer. It would be unethical to give a healthy person a dose of cancerous cells in the hope that the treatment will be successful. As a result, a current cancer patient would have to be used but this still remains unethical. If the researchers are not sure whether the treatment will have any negative implications or not then it would not be ethically right to give the patient the treatment. For example, you need to be absolutely certain that the near-infrared light will not cause any harm to surrounding cells.

Conversely, cancerous cells are in effect immortal and can be kept in vitro and experimented with at all stages of the cell life cycle and even during mitosis. This is a major advantage as cultures of different types of cancers can be grown and tested and then discarded when no longer needed.

Finally, in order to produce antibodies it may be necessary to produce cells that secrete the antibodies. This means that some stem cell research would need to be undertaken. Sources of human stem cells can be found in bone marrow but unfortunately are partly differentiated and can only form a limited type of cell. The 'super' human stem cell can only be found in human embryos and so this raises numerous ethical issues. Testing on human embryos, whose cells have not yet differentiated, is extremely controversial as that embryo has the potential to develop into a child if implanted into a woman's uterus. There are some people who allow the spare embryos to be kept for testing after undergoing In Vitro Fertilisation (IVF) but this is extremely rare and even then, the possibilities are limited. As of yet, there is no satisfactory way of avoiding or overcoming this hurdle.

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