

FUTURE DEVELOPMENTS OF NANOTECHNOLOGY FOR DRUG DELIVERY TO CANCER
CELLS

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ABSTRACT

Nanotechnology is an increasingly important aspect of research. It is the science of manipulating materials on an atomic scale (1). There is a huge potential to use nanotechnology to advance medicine in the upcoming future. There are ongoing studies into how nanoparticles can combat specific biological problems such as free radicals being released during an allergic reaction. Present research is also being carried out into how nanocrystalline silver can be used for the treatment of wounds. Extended contribution to future development is vital as nanotechnology is capable to advance medicine dramatically. This paper will discuss the possible applications of nanoparticles looking in more depth at how nanotechnology can improve the prospects for ovarian cancer and explore the future uses of the relatively new idea, nanotechnology. We will look at how drug delivery can specifically attack diseased cells consequently protecting healthy cells from the drug.

INTRODUCTION

Nanotechnology was first acknowledged in the mid twentieth century by a scientist named Richard Feynman. The American spoke at a Californian conference saying science seems to be "bottomless and in which one can go down and down" (2). These ideas posed by Feynman were further developed by Eric Drexler in 1986. Feynman's studies led Drexler to investigate the physical principles of productive nanosystems. He continued by publishing 'engines of creation' outlining how nanotechnology had the capability to advance medicine, the environment and the economy. Drexler went on to study at depth how molecular nanotechnology can create protein engineering and nanomachinery (3). From this point on nanotechnology become a common source of interest for scientists as many new developments could be made and a whole new area of science was founded. In the 1990's the buckminsterfullerene was discovered by a team of three scientists who used machinery to blast graphite outwards (4). The discovery of this mechanism to create buckminsterfullerene (C₆₀) has enabled scientists to further investigate the uses of nanoparticles particularly in medicine. The uses of nanotechnology in medicine are so useful due to the size of the nanoparticles. Nanoparticles range from 100 - 2500 nanometres (5) whereas a human cell on average is 10 micro metres (6). This enables the nanoparticles to enter cells with little difficulty, delivering the substance required.

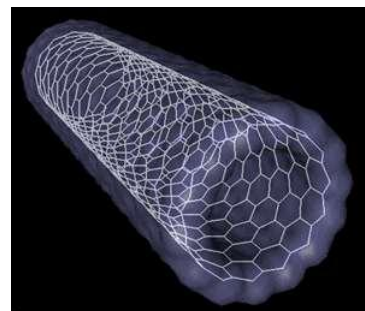
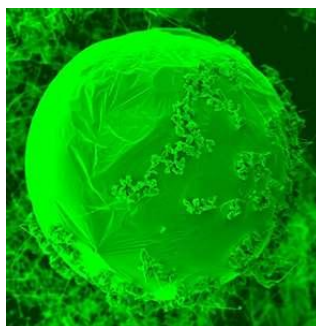
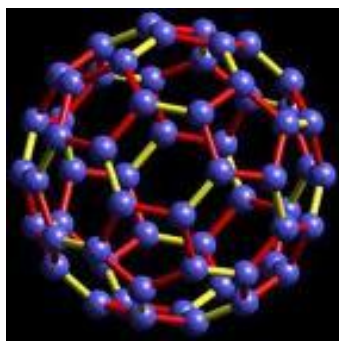


Fig1: Buckminsterfullerene (C₆₀) Fig2: A nanoparticle Fig3: A nanotube which is 100x stronger than steel

Today nanotechnology is widely used in medicine for two particular aspects: imaging and drug delivery. In 1991, experiments began to try and find ways to use buckyballs as possible drug treatments by a researcher named Simon Friedman (4). These investigations are being done to try and combat the common problems with previous methods of treatment. Some of the main problems encountered by previous treatments were intestinal absorption, poor availability of materials, therapeutic effectiveness, side effects and plasma fluctuations of drugs. Presently nanotechnology is being integrated into some aspects of medicine whilst others are still in the process of being tested in labs. So far, the most successful clinical application of nanotechnology experimenting has been wound management. Nanocrystalline silver is being used instead of bulk silver to increase the available surface area directly at a wound (7). This allows more platelets and fibrin molecules to attach to the surface, producing a blood clot sooner. The advantages of this new procedure are that it reduces wound infection, the frequency of dressing changes and consequently reduces pain levels and is more cost efficient for the NHS (8).

IMAGING

Imaging is an extremely important aspect of nanotechnology and a lot of today's research is being directed towards improving medical imaging. It is not a direct substitute for the imaging procedures used presently but intends to develop other methods to add to the accuracy of diagnosis (10). The new technology seeks to target

the diseased molecules in different ways. Rather than using image contrast to identify the diseased cells, they are trying to find a process that can specifically target the actual mechanisms of the disease. This helps the medical professors as it allow them to quickly assess the 'behaviour' of the disease; for example the size, its whereabouts and the speed of its development (10).

However, most of these new techniques of imaging are still in their early stages of development and there are still some issues over the benefits of their uses. Even though it is a big advance in medicine, the present techniques still would have to be in operation and in some cases preparation for the nanotechnology imaging would also have to be done, for example specific and sensitive-site targeted contrast agents (10). Consequently this uses up precious time for the medical staff and it may be costly for the NHS. On the other hand there are countless advantages: the products used are much less toxic than radiation, the method is very user friendly and availability of production is encouraging. The main advantage is that it works in conjunction with drug and gene delivery using nanoparticles (10).

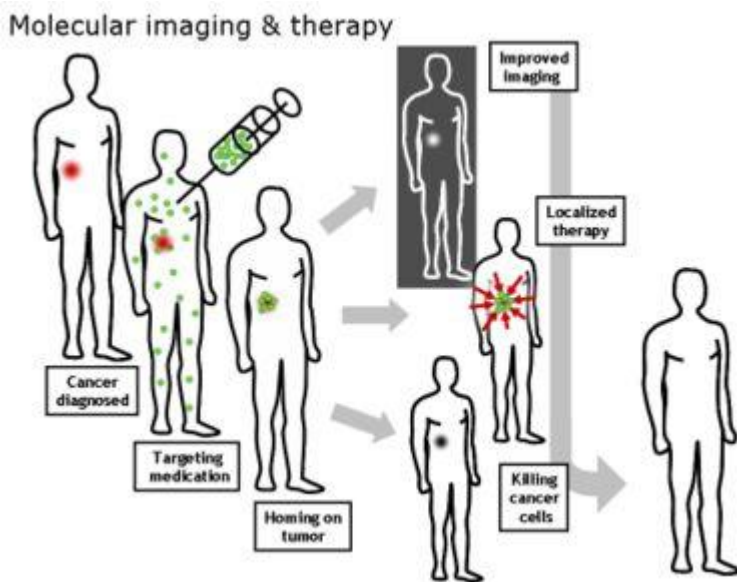


Fig4: Shows the new steps taken in nanotechnology imaging. It shows how it leads onto therapy including drug delivery. (11)

DISCUSSION

There are many possible medical uses for both theoretical and currently used nanotechnology, there are also many current treatments which may prove to be

relatively ineffective compared to the possible nanotechnology developed in the near future. This study focuses on the use of nanotechnology in cancer.

Surgery is one such current treatment, usually only for those with 'solid' cancers. Surgery also offers the best survival rate for people with cancers that haven't spread around the body (30). If the cancer has spread then surgery is often used in combination with other therapies such as radiotherapy and chemotherapy. Even though surgery is common among cancer treatments it is not without its problems, not least the risks of the actual surgery. Bleeding is dangerous and can be caused when working near large blood vessels, even if the doctor is careful in such area there is the possibility of blood loss. Damage could also be caused to internal organs not connected to the cancer, which may cause further complications requiring medical attention.

Chemotherapy is another very common treatment for cancers and is usually described as the use of chemicals in the removal of rapidly dividing cells. While not always applying to cancers, a large proportion of the current chemotherapy treatments are for aiding the removal of them. The therapy has two main groups of chemicals; alkylating agents, which react directly with the DNA, preventing the cell from carrying out certain processes like mitosis, and anti-metabolites, which interact with the processes of cells directly preventing the processes or changing them in a way to stop the cell from dividing.

Melpahalan hydrochloride (alckeran) is one such drug used specifically in the treatment of ovarian cancer, it is combined with thalidomide. It works by adding an alkyl group to the DNA (on the guanine base) of a cell, altering its structure and thus changing the way the cell behaves in such a way that it either cannot replicate or changing its metabolic processes to such a point where it destroys itself. Alckeran's main side effects include nausea, a decreased white blood cell and a decreased platelet count.

There is one obvious problem with such treatments; they do not distinguish between healthy and cancerous cells, meaning they will damage healthy areas of the body as well as the cancer itself. As a result it can reduce the ability to clot blood and can suppress the immune system (20).

A very new type of drug negates the problem of distinguishing between cells, targeting specific mutant proteins found in the mutated cancer cells. This is called targeted therapy (21) - however this does not seem to work on all cancers as not all have the same mutated proteins. Therefore specific drugs are required for different cancers.

Some cancer cells can become resistant to chemotherapy drugs over time, with pumps such as P-glycoprotein (a chemotherapy efflux pump) being used to lower concentrations of cancer drugs in the cell (22). This results in the cancer drugs having less effect on

the mutant cells. As this is a recent discovery, drugs are being developed and began testing in 2007.

Radiotherapy is also used for about 40% of cancers (24) and relies on a cancer cell's inability to repair itself as fast as normal cells. The ionizing radiation emitted from various sources is used to cause damage and destroy the cancerous cells; normal cells around the cancer are also damaged but can repair themselves sufficiently. Many problems are associated with this treatment; one such is actually causing cancer 20- 30 years after treatment (25). Other major side effects include epilation on treated areas with hair loss, cognitive decline, lymphedema and sustained damage to epithelial tissues/ surfaces (25).

In total, current cancer therapies consist mainly of the 3 treatments aforementioned, (chemotherapy, surgery and radiotherapy) and though don't always cure cancer, they have been shown to increase life expectancy for patients for a wide variety of tumours.

New treatments for cancer cells are always needed as many people (more than 1 in 3 (26)) will develop cancer. For example, all malignant neoplasms excluding non-melanoma skin cancer had an incidence of 297,991 in 2007 with 156,232 deaths in 2008. The survival rate for cancer after 5 years in England is low at 44.8% for men and 52.7% for women, suggesting that researching and applying this new nanotechnology is well worth the investment for healthcare in all countries as it contains many advantages.

Fig5: UK mortality rates in 2008 - the 20 most common forms of cancer (9).

Lung	35,261	(22%)
Colorectal	16,259	(10%)
Breast	12,116	(8%)
Prostate	10,168	(6%)
Pancreas	7,781	(5%)
Oesophagus	7,606	(5%)
Stomach	5,178	(3%)
Bladder	5,002	(3%)
Non-Hodgkin lymphoma	4,438	(3%)
Ovary	4,373	(3%)
All leukaemias	4,367	(3%)
Kidney	3,848	(2%)
Brain with CNS	3,674	(2%)
Liver	3,390	(2%)
Multiple myeloma	2,660	(2%)
Mesothelioma	2,156	(1%)
Malignant melanoma	2,067	(1%)
Oral	1,822	(1%)
Uterus	1,741	(1%)
Bone & connective tissue	1,037	(1%)
Other	21,779	(14%)

Advantages to nanotechnology

Research and money is being put into developing ways to deliver drugs with nanoparticles to specific cells of the human body. Hopefully this new procedure will come into common practice in the near future as it has many advantages over the present treatment. The idea of a drug being enclosed by nanoparticles such as buckminsterfullerene is motivated to combat the weaknesses in other procedures.

One of the many downfalls of the present method of drug delivery is poor intestinal absorption (16). In previous drug delivery methods, the encapsulated drug would have had to have been absorbed via the distal small intestine and travel throughout the body before reaching the area of cells in which the drug needs to be delivered. With this new idea of drug delivery using nanoparticles many of these previous obstacles can be overcome. They can now encapsulate the drug so that it is protected against degradation from the enzymes in the stomach and small intestine. This allows more substances to pass through the intestinal tract without being broken down by enzymes (12). Other advantages include avoiding the first pass metabolism of hepatocytes by using an alternative route that avoids the liver, thus increasing bioavailability and being able to transport highly insoluble drugs to target cells (12).

Another major advantage for nanoparticles being used in drug delivery is that they have been programmed in ways to enable it to circulate the bloodstream for an elongated length of time. This allows the nanoparticles such as buckminsterfullerene to release the drug at a much slower rate but continuously (16). This minimizes the fluctuations of plasma in the blood which was one of the most serious downfalls of previous treatments. Plasma fluctuations are the changes to constituent parts in a fixed volume of plasma. The less plasma fluctuations, the fewer side effects are seen on the patient (12). With previous treatment methods, the side effects were often prevalent and often made the patient suffer intensely. If we take as an example, chemotherapy as a previous treatment, it often led to nausea, could be the cause of hair loss and some patients experienced a high fever. Most of these effects have subsided with the new form of drug delivery which makes this method of treatment much more appealing to the patient. It also means that the patient will need fewer drugs as the use of chemotherapy would probably also require anti-emetics (to try and subside the nausea) plus other drugs to try and control the symptoms of other side effects as much as possible.

One of the most obvious advantages to drug delivery using nanotechnology instead of other resources is the size. Nanoparticles are small enough to freely pass through muscles and cell membranes which allows for more efficient delivery of drugs (12). This is important as it means drugs can be given to a patient and the impact measured sooner. This is especially beneficial for patients who are extremely sick and need urgent treatment.

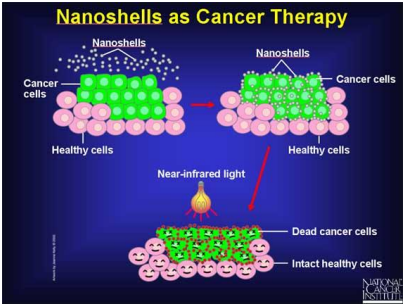
Chemotherapy and radiotherapy are very invasive procedures where a lot of healthy cells are also destroyed in the process of killing the diseased, cancerous cells or tumour. With drug delivery they encapsulate the drug so none of the medicine is released until it reaches the diseased site. This protects the healthy cells but also gives a more concentrated dose to the diseased cells hopefully destroying them quicker.

Nanotechnology is also useful for the pharmaceutical aspect of medicine. It allows drugs to be enhanced and to be developed for the market (12). Some existing drugs can be redeveloped using nanotechnology which gives the drug a longer shelf-life, increase effectiveness, allows them to perform better and reduce the amount it costs the NHS. An expansion of the variety of drugs is very useful as it minimises the resistance of certain cancerous cells to drugs. All of these advantages to drug delivery using nanotechnology that we have discussed in these paragraphs have shown us how medicine can be advanced in the near future. If these new methods of advancing medicine (including drug delivery) were not being explored then medicine today would be less pioneering. This would have a negative effect on medicine as we wouldn't be attempting to correct its many weaknesses.

Methods of treatment

There are many methods of cancer treatment that are under development at present, that if become approved will advance cancer treatment dramatically; reducing pain, side effects and saving more lives. Many delivery methods have passed the phase one stage of being tested on real patients and are currently in the phase 2 clinical trial (13). This means that many methods are nearly fully developed so could be brought into practice very soon.

Delivery Method	Description
Targeted Chemotherapy	Gold nanoparticles are used which are attached to a molecule of a tumour-killing agent called tumour necrosis factor alpha (TNF) and a molecule of Thiol-derivatized polyethylene glycol (PEG-THIOL), so that the immune system cannot pick up the TNF bearing nanoparticle. As the TNF is hidden from the immune system, the nanoparticle can travel through the blood without being attacked. The nanoparticle carrying the TNF only builds up in cancer tumours and not in other areas of the body which means that less damage is done to healthy cells. (14)
Targeted heat therapy through	This drug uses heat therapy to destroy cancer tumours using nanoparticles called AuroShell. These

<p>AuroShell</p>	<p>nanoparticles flow through the bloodstream and exit at the site of the tumour. The nanoparticles then accumulate at the tumour site and concentrate heat generated from infra-red light to destroy the cancer cells. This minimises damage to surrounding healthy cells. (13)(15)</p>  <p>Fig 6: The use of nanoparticles through Auroshell's to destroy cancer cells</p>
<p>Targeted heat therapy for breast cancer</p>	<p>Antibodies that are attracted to proteins which are made in a type of breast cancer cell, are attached to nanoparticles. This makes the nanotubes collect in the tumour. Infrared light is then absorbed by the nanotubes which burns and destroys the tumour. (13)</p>
<p>X-Ray Therapy</p>	<p>This uses the nanoparticles NBTXR3, which are suspension of inert crystalline nanoparticles of hafnium oxide with a coating formulated in water for injection. (17) They can only be activated by X-Rays and when they are they generate electrons which attach themselves to cancer tumours and then destroy them. This method would be used instead of radiation therapy as it offers the benefit of damaging far less healthy tissue. (13)</p>
<p>Targeted chemotherapy through drug carrier</p>	<p>Gold nanorods circulate the bloodstream, exiting at leaking blood vessels where the cancer tumour is. They accumulate at the tumour and infrared light is used to heat it up, which increases the amount of stress related protein on its surface. A liposome (drug carrying nanoparticle) is attached to amino acids that bind to the protein meaning that the increased protein levels at the tumour increases the amount of liposome's so more chemotherapy drug is being delivered to the tumour. (13)</p>
<p>Increasing cancer fighting immune cells.</p>	<p>This method uses nanoparticles containing drug molecules attached to immune cells called T-cells. When the T-cells get to the tumour the drug molecules are released from the nanoparticle, this causes the T-cells to duplicate. The tumour can be destroyed if</p>

	enough immune cells are reproduced. (13)
Magnetic nanoparticles	The magnetic nanoparticles attach to cancer cells in the blood. These enable the cancer cells to be removed before new tumours form. (13)
Nanobubbles	Short laser pulses hit gold nanoparticles to create nanobubbles inside cells. These create small, bright bubbles, which makes them visible under a microscope. These can then be used to diagnose sick cells. (19)
Platinum and gold nanoparticles	Platinum is chemically attached to gold nanoparticles, this flows through the bloodstream safely and enters the tumour cells. The tumour cells engulf the nanoparticles in their endosomes (tiny pockets of cell membrane). The endosomes are very acidic which makes the platinum chemically react to its highly toxic form. (23) This then kills the cancer cells. (13)
Polymer nanoparticles	Polymer nanoparticles are used to deliver the molecule JSI-124 to cancer tumours. The molecule reduces the ability that cancer cells have to suppress the immune system, which slows down the growth of tumours. (13) This treatment has been proved to last for up to a month each time it is carried out. (28)
Iron oxide nanoparticles	Nanoparticles made from iron oxide are coated with a peptide that binds it to the tumour. The iron oxide sends out magnetic waves which MRI scans pick up easily creating clearer images of the tumour. (13) (29)
T2 Biosystems	Superparamagnetic nanoparticles bind the cancer indicating protein and combine together. These then send out a magnetic resonance signal, this shows the presence of cancer related proteins. (13) Cancer could then be detected earlier meaning there would be a greater chance of treating it and survival rates would increase.

Drug delivery to ovarian cancer

Ovarian cancer is a topic of much discussion at present due to the amount of women who are contracting the disease. A lot of research and time is being spent to develop more advanced and successful treatments. Molecules other than drugs for drug delivery can be inserted into the nanocarrier such as imaging agents and antibodies to target specific disease. As well as different substances being placed into the nanocarrier, the

nanocarrier itself can be made up of different materials including: metal or oxide nanoparticles, polymers, liposomes and the material we have been focusing on - the carbon based nanocarriers.

The present detection of ovarian cancer in healthy women is very limited which leads to late detection, usually only once women start to experience symptoms. The screening process as it stands uses a variety of techniques consisting of pelvic examinations, transvaginal sonography (ultrasounds) (18) and measuring the blood serum levels (16). This screening usually only detects the cancer if it is fairly well developed. Screening for biomarkers in individuals who are seen to be at risk are being done on saliva, blood and urine.

The present research is concentrating on developing better techniques to detect the cancer earlier so treatment can begin sooner and survival rates will hopefully then increase. This results in focusing our efforts on enhancing imaging techniques (16) and encapsulating drugs. Research is also exploring ways to piece together proteins, antibodies and microRNA that are all present in ovarian cancer sufferers via samples of urine, serum or tissue biopsies. This will help with earlier detection for future cases.

An area that nanotechnology is hoping to largely improve is the screening of the ovarian cancer. This involves fabricating lab-on-a-chip microfluidic devices for immuno-screening or examining the characteristics of ovarian cancerous cells (16). An example of achievements which have already been made is the growth on cell surfaces with nanodots which was found to differentiate between the different invasive forms of ovarian cancer (16). All of these new and future advances in medicine create huge benefits for a variety of people. The patient will have the most reliable source of information yet and the physicians and doctors can begin their treatment earlier.

The science for improving diagnosis, treatment and aftercare of ovarian cancer is ongoing. Some new processes are in the stages of clinical trials - for instance hormone therapy and gene therapy (27). There may be possibilities in the far future to develop the help available to ovarian cancer sufferers but for the meantime nanotechnology is the most up to date science we have and scientists are trying to advance medicine to its limit with what they have at present. However medicine will never be perfect (it will not be able to save everyone) and there will always be the possibility to develop further.

CONCLUSION

Nanotechnology has great potential for the future of medicine. A lot of money and time has been spent on the drug delivery and imaging aspects to improve the management of

cancer patients. It is still a very new science but slowly these new techniques are being integrated into present medicine.

If many new ideas come forward or complete the clinical trial process in the near future, then medicine could change dramatically for the better. Technology would allow the cancerous cells to be detected at an earlier stage by imaging. If the problem was diagnosed earlier then treatment could begin sooner and the patient would have a higher chance of a good outcome. Imaging would also allow doctors to see the mechanisms of the cancer, for example the behaviour of the cancer and the way it was formed, allowing them to choose drugs that specifically target the root cause of the illness. Treatment can be given at a cheaper cost, and with fewer risks to the patients. Along with the numerous advantages, come the downfalls: it can be costly to research the new treatments when we already have treatment set up that work relatively well. Also some of the new methods of treatment work alongside the current treatments, which leads to more effort, time and money.

Ultimately these new methods are there to save more lives and give the patients a more comfortable way to endure their treatment even if it isn't successful (nanotechnology will never give 100% survival rate). It allows patients the option to choose their preferred treatment which gives them more dignity. In our opinion, nanotechnology is the next step forward to advance medicine.

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