DEVELOPMENTS AND APPLICATIONS OF NANOTECHNOLOGY IN THE TREATMENT OF CANCER

BY

ROSS HORLOCK
ANDREW WALKER

PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2010

ABSTRACT

The science of nanotechnology is a new one, and involves the manipulation and creation of particles and molecules, at the nanonic scale, in order to perform a function. Normally nanoparticles are used in large numbers to fulfil the function allocated to the particles. In the field of medicine, nanotechnology can be applied to the prevention, diagnoses and treatment of disease: by the use of guided drug delivery; new forms of imaging technologies; and in the future the possibility to repair tissue at the cellular level. More specifically, nanotechnology in the treatment of cancer has developed significantly (by increasing the effectiveness of both chemotherapy and radiotherapy), with some completely new ideas for treatments, with several companies already performing clinical trials of new treatments. This paper explores what treatments are currently under development and also what future developments may be.

INTRODUCTION

Over the past few decades, the science of nanotechnology has emerged, granting us the ability to manipulate atoms and molecules (with a size of 1-100nm) with precision. As our understanding and ability to manipulate the world at the nanonic scale grows, so to does the complexity and effectiveness of nanotechnology.

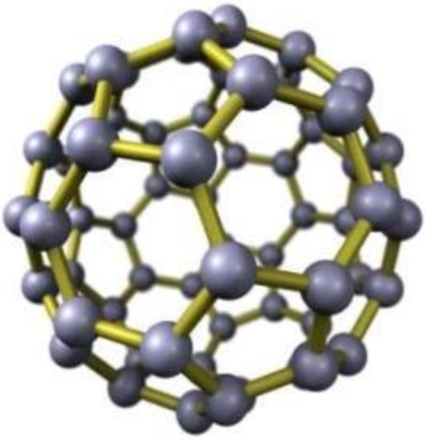

Figure 1

Nanotechnology is an area of science, which has a large influence on many different aspects of modern life. Some such influence can been seen within the electronics industry with the creation of OLED's and nanoparticles capable of generating electricity from the energy of the sun as listed at the website (www.yourguideto.org/nanotechnology). Advancements in nanotechnology have allowed the combination of nanoparticles, to make molecules which can perform a huge variety of different functions. For example outside the realms of medicine, nanomotors and light emitters have been designed.

In the field of medicine, new molecules and applications of nanoscience are just beginning to be used to prevent, diagnose and treat disease. Against cancer, molecules such as Buckminster Fullerene or Buckyballs as they are more commonly known (a sphere of carbon atoms usually composing of around sixty carbon atoms as shown in figure 1) are invaluable discoveries, as inventive new shapes such as this are able to perform variety of useful tasks. For example, a Buckyball has a shape and size which allows it to transport other molecules within the sphere.

As well as creating new shapes, it is also possible to attach another functional molecule to the existing nanoparticle, for instance an antibody or drug. A Buckyball containing drugs used in chemotherapy, when attached to an antibody specific to an antigen present on the cancer cells surface, would attach to the cancer cell only. Drugs used in chemotherapy, for instance topoisomerase inhibitors, could therefore be administered with great precision so that damage to healthy cells would be minimal whilst the cancerous cells would be practically destroyed.

Nanotechnology in medicine is not merely restricted to the prevention of cancer. Other applications are numerous and include the production of insulin by nano "factories" inside the body of diabetic patients. This would mean injections of insulin would no longer be necessary and the patient would be free of the major health risks which accompany diabetes.

Discussion

The treatment of cancer has traditionally been a combination of three different methods: surgery, chemotherapy and radiotherapy. Each of the traditional treatments is currently very crude and can result in damage occurring to the healthy tissue surrounding the cancer. The damage to surrounding healthy cells occurs due to current methods not being targeted specifically to the cancerous cells. However with the application of nanotechnology to these treatments the damage to healthy tissue could be minimised and even totally avoided.

The development of more sophisticated drug targeting using nanotechnology is being applied to the delivery of chemotherapy drugs, with new treatments being tested and some reaching clinical trials. One such new delivery system is Aurimune, a revolutionary new method of delivering drugs used within chemotherapy. The Aurimune delivery system uses colloidal gold nanoparticles as a core to which the therapeutic and targeting mechanism are attached. The targeting molecule being trialled with Aurimune is tumour necrosis factor alpha (TNF), a protein used within chemotherapy. The TNF is attached to colloidal gold nanoparticle with Thiol-derivatized polyethylene glycol (PEG-THIOL), a chemical that prevents the Aurimune being detected by the body's immune system as well as the chosen therapeutic.

The Aurimune is injected into the patient where the colloidal gold nanoparticles accumulate at the site of the tumour. The Aurimune particles are too big to diffuse across the walls of the blood vessels as such minimizing damage to healthy cells. The Aurimune is however able to leave the blood vessels at the site of the tumour as the new blood vessels around the tumour are leaky allowing the Aurimune to accumulate at the cancerous cells, delivering the chosen therapeutic and thus killing the cells.

Evidence for the effectiveness of Aurimune can be seen in figure 2 where the healthy tissue on the right half of the photo has no black dots indicating a minimal build up of the drug, if any build up at all. The tissue sample on the left half of the photo however is cancerous and shows many black dots where the Aurimune has accumulated in the cancerous tissue showing the effectiveness of the new delivery system to target the area of a tumour.

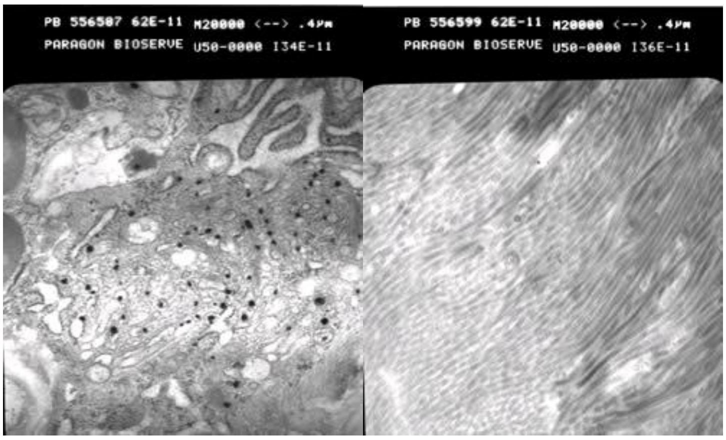

Figure 2

This method of drug delivery is still rather crude and wouldn't be a feasible method of treating cancers in important organs such as the lungs or liver as there is still a large probability of the therapeutic affecting healthy cells within the immediate area. The new technique of Aurimune does however provide a quantum leap in the targeting of chemotherapy drugs, as the drugs no longer affect the whole body but rather only affect the tumour cells and the immediate surroundings.

Other advances in drug delivery using nanotechnology have come with the discovery of dendrimers. Dendrimers are small globular molecules produced by branching two monomers in a repeating pattern to produce generations, which are the same polymer at different sizes, as shown in figure 3. The advantage of this characteristic is that dendrimers can act as a base unit much like the colloidal gold in the Aurimune, however with the use of dendrimers multiple aspects could be attached such a the following: an antibody for targeting; a therapeutic to cause damage to the cancerous cell; a marker to allow the tumour to be seen by a form of imaging technology such as an MRI scan.

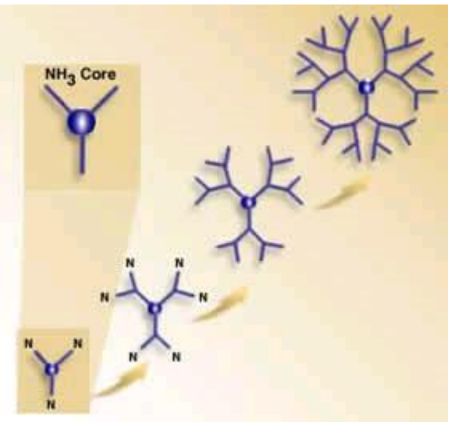

Figure 3

The possibility for the use of dendrimers comes not only from the ability of dendrimers to attach to multiple chemicals, but also due to the ability of dendrimers to be formed from a variety of compounds and monomers which currently have no known adverse affects on the body, such as disrupting metabolic processes or inhibiting enzymes.

Dendrimers also have the possibility of being more than just a targeting system for cancer but rather a preventative measure. The prevention would come from receiving an injection of dendrimers as a precaution, where the antibody attached to the dendrimer targets antigens found on a cancer which the person is known to have high risk of, due to family history such as a history of breast cancer. Attached to the cancer would be a therapeutic, which prevents cell division such as a Vinca alkaloid. By using such a combination the dendrimer would be able to move through the body’s circulatory system until the antibody attached to the specified cancer, and the dendrimer was absorbed into the cell by a cell receptor mediated uptake. By preventing the cell from performing mitosis the possibility of a tumour forming is decreased and the cancerous cell could simply be destroyed by a second therapeutic attached to the dendrimer designed to kill the cancerous cell such as an anti-metabolite.

Targeting chemotherapy isn’t the only problem when it comes to treating cancer. Currently some extremely strong therapeutics can only be administered intravenously, preventing people from receiving treatment at home. Likewise if antibodies were to be used as targeting agents the antibodies would be digested in the stomach due to antibodies being proteins. These issues could potentially be overcome by the use of nanotechnology within oral delivery of drugs.

There are two main approaches to solving the problem of oral drug delivery. For the more potent therapeutics the issue comes in solubility and absorption into the body via the epithelial cells of the small intestine. Both the solubility problem and absorption problem have started to be solved by research carried out at the Johns Hopkins University School of Medicine where a nanoparticle which is a polymer consisting of six parts; N-isopropylacrylamide, two parts methylmethacrylate, and two parts acrylic acid was created as a means to transport the more powerful therapeutics through the small intestines epithelial cells. This new polymer was designed to lodge within the mucus lining of the small intestine thus increasing the chance of the therapeutic being absorbed and released into the blood stream without the need for any injections or visits to the hospital.

This new polymer could not only be used to administer the basic drug but also there is a possibility to harness this break through as a means of administering targeted treatment where the targeting factor is an monoclonal antibody which would otherwise be digested in the stomach due to the antibodies being proteins. However, if the targeted therapeutics were placed within these polymers then the administration could be oral and targeted, thus allowing the patient to receive treatment at home. This would ensure the patient would receive the most effective and accurate treatment.

The second possible method of oral administration is the use of small lipid vesicles. Lipid vesicles are not new in terms of the ability to manufacture the vesicles, however what is new is the ability to produce lipid vesicles which are durable and withstand the fusion of other lipid molecules. This advance occurred at the University of Illinois where charged nanoparticles were introduced to the membranes, which allowed the membranes to withstand further fusion whilst preventing the membranes from bursting and leaking the chemical contained within.

The development of stable lipid vesicles could be used to administer larger targeted chemotherapeutics via oral administration. This ability would come from the membrane, preventing the targeted drugs being digested, as the membrane cant be digested until the small intestine. At this point the drugs could be absorbed into the epithelial cells of the small intestine. Even the membranes, which don't get digested, could still successfully administer the chemotherapeutics by fusing with the cell membranes of the epithelial cells. This would provide a new method of oral administration without the risk of possible toxic chemicals forming from the decomposition of the lipids.

Nanotechnology has the potential to completely revolutionise the way cancer is treated, with brand new molecules and techniques. However nanotechnology is also an extremely effective means of improving current methods and technologies already in use today. The ability of nanotechnology, to eliminate, or at least reduce many of the risks associated with the treatment of cancer using radiotherapy, has the potential to revolutionise cancer care. In particular, nanotechnology can limit the damage caused by radiotherapy to healthy tissues of the patient.

Radiotherapy is an effective technique used to kill cancerous cells. Unfortunately it is currently impossible to be exactly accurate with the radiation used, and the destruction of healthy cells is unavoidable. Nanotechnology is being developed however, which allows for the amplification of the effect of radiotherapy in the tumour only, leaving the surrounding tissues with only a standard dose of radiation or a dose of safe electromagnetic waves such as infra red. The potential of the new technologies would be the patient getting excellent results without having as many radiotherapy sessions as a traditional treatment plan.

The company Nanobiotix has already developed an improved from of radiotherapy using nanoparticles, which form free radicals within the cancerous cell when activated by x-rays. The particle used is inert, and therefore is harmless until activated by an x-ray dose. It is technically therefore not classed as a drug as the nanoparticles don't constantly have an affect on the patient. The particle used by Nanobiotix has an unreactive layer surrounding a core comprising of nbtxr3 nanoparticles (figure 4), which makes sure that the particle will not react inside the body. The core of the particle is the component that once activated by the x-rays emits cancer-destroying oxygen free radicals. Due to the technology being an improvement of current techniques it can work using current radiotherapy equipment.

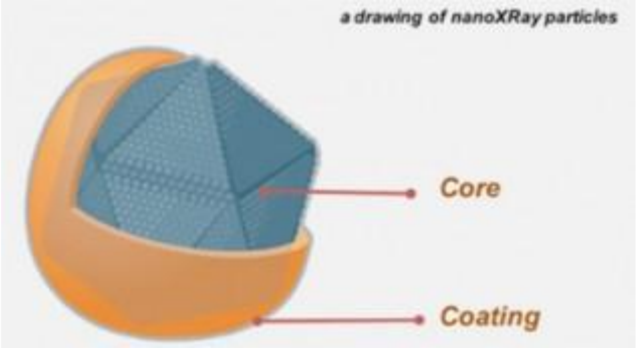

Figure 4

Therefore it would mean hospitals would not have to pay large sums of money for new equipment.

The nanoparticles used are specifically designed to accumulate only in a tumour, but the x-ray dosage can still potentially damage surrounding healthy cells due to the ionising affect of x-rays. This new technology has already been proven successful in preclinical studies according to the company’s website.

These current methods however merely enhance an existing method of treatment. Nanobiotix states on its website that the particles would be injected directly into the tumour, however as the particles are unreactive, a theoretical use of this molecule could be to inject it into the bloodstream, with a method of ‘finding’ cancerous cells (i.e., an antibody, corresponding to an antigen on the tumour cells surface, affixed to the surface of the nanoparticles). As the antibody is specific, it would bind only to specific tumour cells. This method would have the advantage of catching a specific cancer which had spread to other parts of the body. However it would also mean a whole-body x-ray would be necessary to activate the particles within the cells. This full body scan would mean a lot of potential damage to healthy cells, which would defeat the objective of new technology. There is also risk of the particles breaking down in unaffected areas and causing damage or somehow accumulating in a place where high levels would be potentially dangerous, for instance in the brain. These disadvantages all lead to the conclusion that a treatment such as this would require an alternate method of activation other than x-rays.

A very different molecule that also uses nanotechnology consists of a molecule of hydrogel, which behaves like a tiny lock by liquefying in the presence of light and solidifying without the presence of light. This non-toxic molecule would not kill non-cancerous cells by bombarding them with free radicals, but would instead kill the cancerous cells by clasping shut blood vessels supplying the tumour with nutrients vital for survival, according to researchers at the University of Florida. This technology (although still only in the very early stages of development) has many advantages over traditional radiotherapy. One is that the damage to healthy cells would be almost nonexistent, and another is that although it still uses electromagnetic radiation to be activated, it is harmless light that acts as a trigger for the molecule. Unfortunately this treatment is years away from a realistic method of cancer treatment. It is however, a good target for future techniques aiming for minimal interruption to the surrounding cells.

A new technology being developed at MIT, which sounds similar to the methods mentioned earlier but is in fact completely different, is one involving magnetic fields instead of electromagnetic radiation. Obviously this type of activation is ideal for use inside the body, as not only is it easy to penetrate deep within tissues and organs, it is also completely harmless, as long as the patient has no metal replacements of body parts. This technology does not even pose any risk to healthy cells once activated, as it does not actively destroy the tumour as other treatments do. Instead, it merely attaches itself to the tumour cell, and then separates it from the healthy cells when stimulated, where the malignant cells can be collected and destroyed separately outside of the body.

However this type of treatment, as well as only being in very early stages of research and development (as with many nanotechnologies at the present time), would seem unlikely to be effective against large, advanced tumours. At the very least it would be expensive, and the number of particles needed would be vast. However, the fact that this technology causes no damage to host cells is a massive advantage over other methods of treatment, as it means fewer side effects for the patient, which therefore means less discomfort. Therefore this technology would seem to have the most potential to revolutionise the treatment of cancer in the future.

An ideal method of treatment would be one which combined the powerful tumour killing abilities of the x-ray activated nanoparticles, with the safety of the light activated and magnetically activated particles. In fact, a hypothetical treatment in the future could be to use all three in tandem to maximise the treatment effectiveness. Clamping molecules activated by light, operating simultaneously with the cancer-killing x-ray activated particles, could cut off blood from the tumour and destroy the bulk of the malignant cells. Then the magnetically activated particles could be used to remove any surviving cells, which would therefore totally eradicate the tumour with minimal loss to healthy cells of the patient.

One potential problem with this is that the different activation methods for the particles could interfere with the other particles involved. For instance, x-rays used to activate one set of particles may destroy or change a different type of particle, rendering it useless, or even harmful. Also the particles may inadvertently destroy each other after activation, instead of destroying the tumour. To be effective, the particles may need to be re-designed to be compatible with each other.

A final possible method of cancer treatment is to use carbon nanotubes. Carbon nanotubes have two key properties, which would make them an effective tool to treat cancer. The first important property is that nanotubes are extremely small, about the same size of half the width of a DNA molecule. The second important property is the nanotubes heat up dramatically when electromagnetic radiation, in between the infrared and visible light spectrums, is shone onto the nanotubes.

The ability for nanotubes to be able to heat up has been used by a research group at Stanford to treat cancerous cells. The cells are targeted by the carbon nanotubes being coated in folate molecules (this is a molecule cancerous cells have more recptors for than normal cells). The folate molecules then cause the nanotubes to be absorbed by the cancerous cells. Shining a laser that produces radiation near-infrared light can then kill the cancer, due to the nanotubes absorbing the radiation and emitting heat. This treatment has the added benefit that the radiation is harmless and can pass through tissue such as skin and muscle without damaging the healthy cells.

Conclusions

The discussion has shown how nanotechnology is aiding the treatment of cancer by targeting both the radiotherapy and chemotherapy aspects of treatment, however so far the treatment of cancer has not been done so that one molecule could be used to provide chemotherapy and radiotherapy simultaneously. This possibility is very real, as due to advances such as dendrimers, carbon nanotubes, monoclonal antibodies and nanoXRay particles, a molecule that combines both chemotherapy and radiotherapy into one treatment may be a possible solution. A dendrimer molecule could act as a core from which a chemotherapeutic as well as either carbon nanotubes or nanoXRay particles could be suspended on. The dendrimer could then be attached to an antibody or other targeting molecule to then target the cancerous cells. The molecule would then be able to deliver a chemotherapeutic to damage the cancerous cell and then the cell could be completely destroyed by the use of one of the new forms of radiotherapy involving the use of either x-rays or the near-infrared light segments of the electromagnetic spectrum.

This molecule could have great potential; however tests would have to be carried out to ensure the various components wouldn’t react to form toxic products which could damage healthy tissue. This form of treatment would also have the problem of leaving behind a dead cell from which the genetic material could move into other cells causing them to become cancerous. As such although the theory behind this form of treatment could produce a new potential cure for some cancers, there are still many practicalities to overcome.

Earlier in the discussion the possibility of combining various nanoparticles used in radiotherapy to form a three-pronged offensive was discussed. This method could produce a simple solution however as stated before there is the possibility of the nanoparticles reacting to the different forms of radiation with unknown side effects. The potential for these side effects to occur would require further research into how each particle behaves under the use of the various radiations and then into how the particles interact with each other.

From the contents of this paper we have discovered there are many possibilities of applying the use of nanotechnology to the treatment of cancer. Many of these possible treatments involved targeting the cancerous cells more efficiently, and a few of the treatments use less invasive techniques to prevent damage occurring to the healthy surrounding tissues. All these possible techniques have the potential to become an invaluable tool in treating cancer and could potentially be spread to other aspects of medicine.

References

Nanotechnology in Cancer Treatment
http://www.understandingnano.com/cancer-treatment-nanotechnology.html

What is nanotechnology
http://www.cancer.gov/cancertopics/understandingcancer/nanodevices

Current uses of nanotechnology at or near market
http://www.yourguideto.org.uk/nanotechnology/nanotechnology-uses.htm

Tumor Targeted Therapies
http://www.cytimmune.com/go.cfm?do=Page.View&pid=17

Dendrimers Introduction
http://nano.med.umich.edu/Platforms/Dendrimers-Introduction.html

What is nanoXRay
http://www.nanobiotix.com/technology-products/

Nano lock technology
www.medicalnewstoday.com

Drug-delivery system designed for hydrogel
http://apps.research.ufl.edu/otl/pdf/marketing/12527.pdf

Nanotechnology and Magnetism Partner Against Cancer
http://medgadget.com/archives/2008/07/nanotechnology_and_magnetism_partner_against_cancer.html

Nanotech-laser treatment that kills cancer cells without harming healthy tissue
http://news.stanford.edu/pr/2005/nanotube-08105.html

Figure1
http://www.sciencedaily.com/releases/2008/03/080320095005.htm

Figure 2
http://www.cytimmune.com/

Figure 3
http://nano.med.umich.edu/

Figure 4
http://www.nanobiotix.com