Exploring the Advancements in Nanotechnology which are leading to new ways of Diagnosing and Treating Cancers

BY
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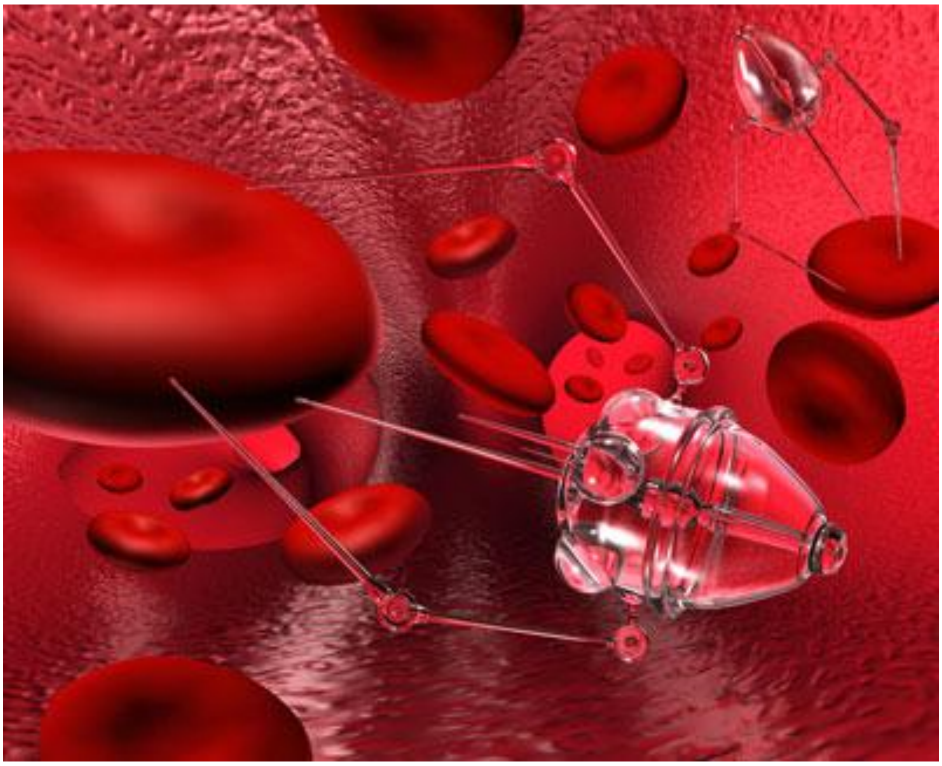
PASS WITH MERIT



The possible future of cancer treatment?

RESEARCH PAPER
BASED ON
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Abstract

Nanotechnology is at the cutting edge of modern science. Advances in microscopy, such as the atomic force microscope and the scanning tunnelling microscope, allow us to image and manipulate matter at the atomic level. New contrast agents that significantly improve the resolution of MRI and CT are being developed. Better treatments are being developed which are targeted to cancer cells. This article will explore these current developments as well as possible future developments in the use of nanotechnology to treat cancer and save lives.

Introduction

The prefix nano- is derived from the Latin word nanus, meaning dwarf, which is derived from the Ancient Greek word, nanos or νανος. In modern science the prefix nano- means 10^{-9} so a nanometer is 10^{-9} meters. This is the atomic scale, with one atom being 0.1 nm in size. The first papers considering nanotechnology for use in medicine were published in the early ‘90s and the first treatments for cancers using nanotechnology emerged not long afterwards with drugs such as Doxil[1], pegylated liposome-encapsulated doxorubicin. This greatly reduced the potentially lethal effect doxorubicin can have on the heart.

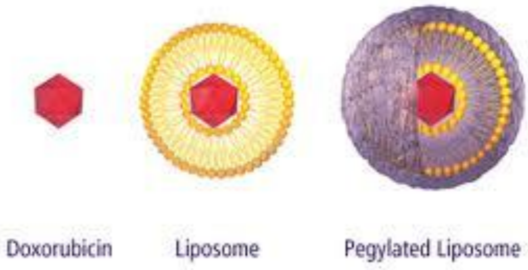

Figure 1: Doxil is one current way nanotechnology is being used to treat cancer

Another example of how nanotechnology is leading to new cancer treatments is AutoLase®[2] which uses nanoparticles, specifically designed to absorb near-infrared radiation and convert it to heat, to reduce or destroy tumours. A final example of how nanotechnology can be used to diagnose cancer is the use of iron oxide nanocrystals with superparamagnetic properties which are used as contrast agents in MRI.[3] The nanocrystals are very effective contrast agents and, more importantly, can be combined with monoclonal antibodies or other such proteins to lock onto cancer cells. Research has also been conducted which suggests they are readily taken up by lymphocytes and can thus detect lymph-node metastases non-invasively when used in conjunction with MRI.[4]

Why is all this important? Why do we invest hundreds of thousands of pounds into developing these new cancer treatments? First of all cancer is a big problem, especially as we are all living longer. 297,990 new cases of cancer were diagnosed in the UK alone in 2007 and the odds of someone developing cancer over the course of their lifetime is currently quoted as one in three.[5] World-wide there were an estimated 12.7 million new cases of cancer in 2008. But the scale of the cancer is not the only problem. Current cancer treatments can be extremely unpleasant and are not always effective, particularly as cancers are often only detected when they become symptomatic and thus quite advanced. Chemotherapy leads to potentially dangerous immunosupression in almost all current regimens as well as fatigue, hair loss, nausea, vomiting with a further risk potential damage to specific organs depending on the drug used. Radiotherapy has its own side effects including damage to the skin, swelling and damage to underlying organs surgical intervention, before treatment by radiotherapy or chemotherapy, carries with it all the risks of surgery. The nanotechnology technology outlined in the following paper may have the potential to change all this.

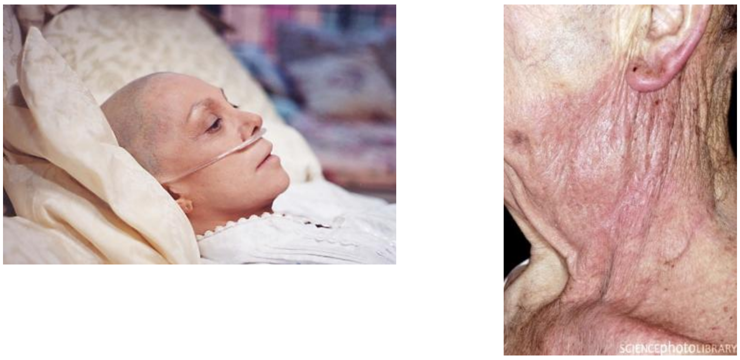

Figure 2: Left is a patient exhibiting the typical side-effects of chemotherapy. Right is a patient exhibiting skin damage due to radiotherapy

Discussion

The aim of cancer treatment is to eradicate the tumour with minimal or, ideally, no damage to the patient, at as low a cost as possible. While this can be achieved with skilled surgery followed by radiotherapy or chemotherapy if the cancer is diagnosed early enough or, in the case of lymphomas and other highly radiosensitive cancers, radiotherapy alone, it is often impossible as the cancer has already metastasised or invaded neighbouring tissues prior to diagnosis. In this situation surgery, followed by chemotherapy and/or radiotherapy, is used to control the cancer and its symptoms. Cancer and its treatment can often severely impact on a patient’s quality of life for months or years before it is finally eradicated or the patient ultimately dies. The important questions to ask here are: why does cancer take so long to diagnose? Why is the treatment so dangerous? Why is the treatment not always curative?

Cancer is difficult to diagnose. It is an insidious disease that can be dormant and undiagnosed for weeks, months, even years. While it is dormant the patient will show no symptoms allowing it to carry on living a normal life but the cancer is still growing inside them. The primary tumour, that is the first cancer tumour to develop, will gradually become symptomatic and be detected and treated appropriately. This in itself is not a problem, what is a problem is cancer’s ability to metastasise to distant parts of the body undetected. A classical example of metastasis is breast cancer which spreads to bone. The primary tumour in the breast grows until the patient notices, it is then removed by surgery and radiotherapy or chemotherapy are given to hopefully eliminate any other cancer cells which were not removed via surgery. 10 years later the same woman has a minor fall and fractures a bone, typically the neck of the femur. She is then diagnosed with metastases of her breast cancer within her bones. If cancer treatment is to be effective, earlier diagnoses are vital along with more effective post-treatment screening for metastases. Nanotechnology offers ways of improving the contrasting of cancer cells in vivo and improving the resolution of MRI. This will allow current imaging techniques, such as MRI, to see tumours that are difficult or impossible to see at the moment. It will also lead to new imaging techniques altogether.

There are two ways of using these particles to target a tumour, passive targeting and active targeting. Passive imaging relies on both the size of the nanoparticles used and a phenomenon of tumour vasculature known as enhanced permeability and retention effect (EPR). EPR occurs because, as a tumour grows, it needs to grow new blood vessels from existing ones to keep it supplied with blood. This is known as angiogenesis. However, the angiogenic blood vessels grown are ‘leaky’; they have gaps between the adjacent endothelial cells which can be as wide as 800nm.

This allows nanoparticles to pass out of the blood vessels and into the tumour tissue, leading to a concentration of nanoparticles inside the tumour cells, because the nanoparticles are small enough to be taken up by cells. Active imaging coats the nanoparticles in antibodies or other molecules that bind onto cancer cells whenever they encounter them. Nanotechnology offers many ways of improving imaging for cancer. The leading techniques currently being researched are: quantum dots, nanoshells and paramagnetic particles.

Quantum dots are semiconductor nanocrystals encased in a metal shell, which can fluoresce, giving them a broad potential for use in various applications in the research, management, and treatment of cancer[6]. Quantum dots are particularly useful for medical imaging because they target a tumour passively or actively and they possess several unique properties no organic fluorphore can match. These properties include a wide fluorescent emission spectra from 2000-400nm, being tuneable to emit specific discrete wavelengths of light and are an order of magnitude more resistant to photobleaching than organic fluorphores.[7] Quantum dots can be prepared to all respond to one light source but emit different wavelengths of light, which allows for different targets to be labelled independently. These properties may improve the sensitivity of molecular imaging and quantitative cellular analysis by 1 to 2 orders of magnitude.[8]

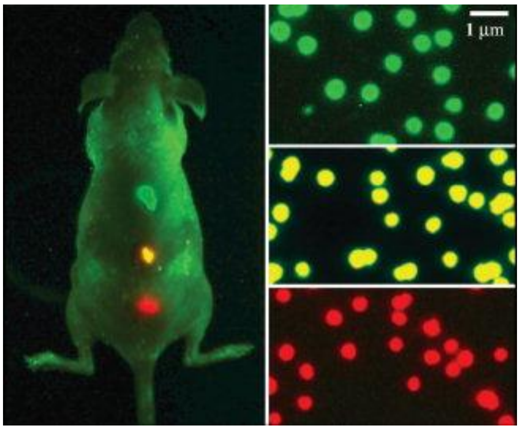

Figure 3: Highlighting the ability of quantum dots to fluoresce at different wavelengths when exposed to the same light source.

However quantum dots have one major disadvantage. Almost all currently produced quantum dots need to contain heavy metal crystals such as cadmium in order to function and the quantum dots are known to break down upon exposure to UV light, releasing the heavy metal into the blood stream. Thus there are questions about their safety. It is known that polymer-coated quantum dots are more stable but, as the exact mechanism of the release is not known, it cannot be said for certain that they are safe. Work is being done to produce quantum dots of the same quality which do not contain heavy metals. It is unlikely that quantum dots will be used in human patients until further studies are conducted into the stability of quantum dots, which conclusively prove they are stable when coated in a polymer such as poly(ethylene glycol) (hereafter PEG) or heavy metal free quantum dots are produced in bulk.

Nanoshells are another extremely promising development in the imaging of cancer because they appear to have similar imaging properties to quantum dots without any potential for heavy metal toxicity. They consist of a dielectric core encased in a thin sheet of metal and plasmon-mediated conversion of electrical energy into light is responsible for their emissions. They are tuneable to emit discrete frequencies in the same way as quantum dots and can emit across a similar spectrum from ultraviolet to infrared. Like quantum dots they can actively or passively target a tumour and can be concealed from the mononuclear phagocyte system (hereafter MPS) using PEG. Nanoshells can also be used as a contrast agent in various forms of tomography. One potential limitation on nanoshells is their size. Nanoshells can be anywhere from 10-300nm in size, while quantum dots are only 2-10nm in size. Nanoshells also have very interesting therapeutic properties, which will be discussed later.

Paramagnetic nanoparticles are nanosized MRI and CT contrast agents. They are being avidly researched at the moment because they possess far greater magnetic susceptibility than any traditional contrast agents. This means paramagnetic nanoparticles offer an image with far greater resolution than existing contrast agents. Superparamagnetic iron oxide particles are the most researched of these contrasts agents and can be produced in two different sizes. The first size is quite large, 50-100nm, and particles of this size, when administered intravenously, are rapidly taken up by the liver. This property makes them useful for diagnosing hepatic cancers. The second size is much smaller, 5-10nm, which allows them to enter the bone marrow and the lymph nodes.

The next question to answer is why current cancer treatment is so dangerous? The answer is quite simple. Chemotherapy is the administration of cytotoxic drugs which impair mitosis and thus kill rapidly dividing cells. This treatment is given systemically and thus all rapidly dividing cells in the body are affected by the chemotherapy, from nails to hair to blood cells as well as the cancerous cells. The drugs can also affect specific organs, as mentioned earlier. This also means chemotherapy, particularly if it is used after surgery, is hit and miss. The remaining cancer cells may or may not be caught. However, due to advances in nanotechnology, chemotherapy can be targeted to the cancer itself, which makes the treatment far more effective and reduces the effects on the rest of the patient’s body. This is done by placing the cytotoxic drugs inside a nanovehicle. The nanovehicle can be anything from liposomes to nanoshells.

The nanovehicles target the cancer in the same way as the imaging nanoparticles, though nanovehicles can also use the unique micro-environment of the cancer cells to target cancer and then control the drug release. There are many different candidates for use as nanovehicles: liposomes, which are already used in existing drug therapies, micelles, dendrimers, nanoparticles, protein cage architectures, to list but a few.[9]

The first task for any nanovehicle, or any nanoparticles at all for that matter, is to evade clearance by the MPS and the liver, unless the lymphatic system is the target in which case take up by the MPS may be good but that is beyond the scope of this article. This is done using the so-called stealth polymers, such as poly(ethylene glycol), which have been mentioned in passing throughout this article. Poly(ethylene glycol) and other stealth polymers conceal the nanovehicle because they absorb so much of the surrounding water that they appear, as far as the MPS and the liver are concerned, to be water. The body’s clearance mechanisms cannot tell the two apart. This can allow nanovehicles to stay in circulation for as long as a day before the renal system clears them from the blood and into the urine. This, hopefully, gives the nanovehicles enough time to reach the tumour.

The second task is to know when to deliver the drug and where to target. This has been and is a huge problem for medical researchers. Developments in understanding the biochemistry of blood and cancer cells have allowed various types of targeting molecule to be developed with varying degrees of success. The ones most commonly mentioned in research at the moment are ligands. Ligands are substances that form complexes with biomolecules. In the case of targeting cancer it forms a complex with biomolecules unique to the type of cancer targeted. These targeting ligands can compromise the stealth polymers and thus leave the nanovehicle vulnerable to clearance by the MPS. Recent research by BIND Biosciences has suggested a way round this.[10] The founders Robert Langer and Omid Farokhzad have discovered that reducing the number of targeting ligands can lead to an increase in effectiveness, compared to the traditional method of placing as many ligands as possible on the surface of the nanovehicle. This allows the nanovehicle to target cancers effectively, without losing its stealth capabilities. So the nanovehicle knows where and what to target but not when to release the drug. Again, as with the targeting, many different techniques are being pioneered to allow the drug to be released at the correct time with the correct dose. One technique, which uses passive targeting, uses the cancer cell's own unique microenvironment against it, as mentioned above. This works by attaching a tumour-specific molecule to the drug which is contained in a liposome.[11] The liposome dissolves upon entering the cell releasing the inactive drug which then activates as the bond attaching tumour-specific molecule to it breaks, destroying the cell. This technique showcases one method of delivering chemotherapeutic drugs specifically to the cells they are suppose to target. One other technique is to use the process of binding onto the cancer cell to provide the energy to change the shape of the nanovehicle, delivering the drug. These techniques minimise the side-effect profile of the drug and thus the side-effects and risks associated with chemotherapy and maximise the dose the tumour receives.

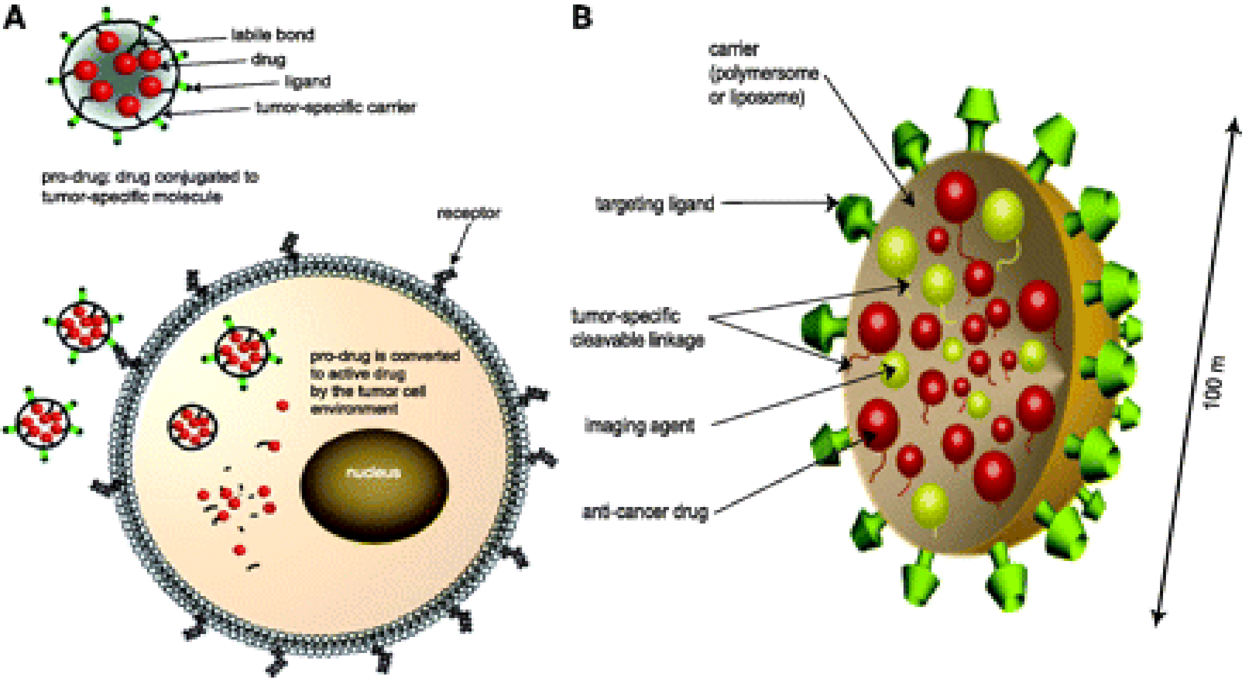

Figure 4: one potential delivery system being researched that delivers chemotherapeutic drugs directly into the cancer cell

Radiotherapy could also be aided by nanotechnology, or rather replaced by a new process known as photoablation. Photoablation uses specially engineered nanoshells to amplify a near infra-red beam. This process creates heat which destroys the cancer cells but, because the nanoshells are inside the cancer cell, surrounding normal cells are not affected. These nanoshells can again target the cancer cells actively or passively. This, combined with improvements to imaging and the potential changes to chemotherapy outlined above, is a significant development indeed.

Conclusion

The final question was: why is cancer treatment not always curative? That question has actually been answered throughout this paper. Cancer is difficult to diagnosis, secondary tumours, or rather the single or small bundles of cells that cause them, are neigh on impossible to detect and thus must be treated blindly blasting the patient's body with cytotoxic drugs or radiotherapy. Specialist surgery is our best weapon against cancer at the moment but the precise art of removing a tumour, with no remainder, from any part of the body is difficult and sometimes simply is not an option. But that is not really the final question. The final question is can nanotechnology really change any of this? Cancer treatment has been the prime example of the importance and extraordinary capabilities of nanotechnology yet only a handful of new cancer drugs using nanoscale delivery systems are in operation. It is difficult to mass-produce nanoparticles reliably to deliver drugs. Admittedly nanotechnology has led to breakthroughs in diagnosing cancer but is it time for a reality check on its therapeutic abilities? I would say it is not. Medical research takes time and money, especially when it is into such complicated subjects as oncology and nanotechnology. New treatments are entering into clinical trials now as are new diagnostic tools. It seems that we are on the verge of a breakthrough in nanotechnology. But hasn't it been like this before? The answer is no. Click chemistry, a concept only unveiled ten years ago, is now being applied by BIND Biosciences to produce nanoscale chemotherapeutic drugs. Autolase® is in clinical trials and proving very successful both on its own and combined with other therapies. There will be problems along the way. The Autolase® therapy may not be effective for all cancers and BIND Biosciences breakthroughs may have been exaggerated. As these breakthroughs are relatively recent only time will tell if these and other research programs finally make it into widespread clinical use, though Autolase® is nearly there. But I think that past failures make it all too easy to be pessimistic of these breakthroughs, when they could be about to change oncology forever. It is unlikely that we will have the wonderful nanomachines shown on the front cover exterminating disease wherever they find it in the near future, if at all. But I think we will find new more effective cancer treatments that are able to provide curative treatment to those cancers which are currently difficult or impossible to cure.

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Figure 1- Left image http://ovariancancersymptom-s.com/chemotherapy-side-effects/ Right image http://www.sciencephoto.com/images

Figure 2- http://biotech.about.com/b/2009/07/14/johnson-and-johnson-not-just-baby-powder.htm

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