The Use of Nanotechnology in the Treatment of Cancers

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PASS WITH MERIT

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ABSTRACT

Interest in nanotechnology and it's development have increased increased exponentiallly over the last few decades, from the 1959 Feynman's "plenty of room at the bottom" speech, to the construction of carbon nanotubes, inspired by the Nobel Prize winning discovery of buckminsterfullerene. The term nanotechnology was coined to mean engineering at a sub micrometer level, to the scale of nanometres (1×10^{-9} metres). Nanomedicine is the medical application of nanotechnology and is an area of extensive and largely untapped research within the medical sciences. This paper aims to describe and explain principles and discoveries within nanotechnology as well as delve further into current and potential areas of research within nanomedicine, concentrating on nanotechnology in the treatment of cancers.

INTRODUCTION

WHAT'S ALL THIS THEN?

Before we can fully understand current and potential areas of research and application of nanomedicine, we must first understand the development and basic principles of nanotechnology. In a nut shell, nanotechnology is the manipulation of matter at a molecular level. This can be achieved either by physically handling molecules, using laser tweezers and an atomic force microscope, or by using self-assembly approaches. Both techniques allow for the construction of new materials between 1-100nm in size (1×10^{-9} to 1×10^{-7}m). Figure 1 should help to visualise the sheer extent of how small we are actually talking here. Most nanoparticles are no larger than one thousandth of the diameter of a human hair.

HOW DO THEY MAKE 'EM?

Constructing and fabricating nanomaterials can be a tricky and laborious process. There are various approaches that have been developed over the years but the best known and most used is the bottom-up approach. Bottom-up approaches use the idea in nature of making larger objects from many much smaller objects. (E.g. atoms → amino acids → primary structure polypeptide chain → tertiary structure protein). This approach is achieved by self assembly. Self assembly is another idea taken from nature and a key example is protein synthesis, by transcription and translation of RNA, producing a polypeptide chain of amino acids. It relies on signals from various chemical reactions to work, and can be very complex. This process is of course difficult to conceptualise, but it means there is a much smaller chance of error.

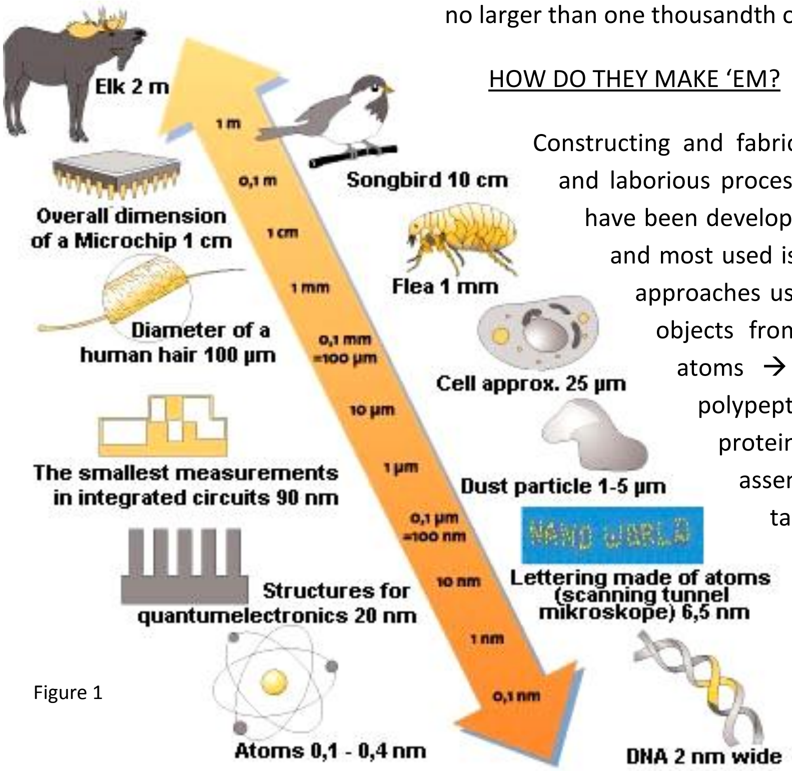


Figure 1

SO WHY NOT JUST USE REGULAR MOLECULES?

Nanoparticles and nanomaterials are structurally different from normal molecules and so they also have very different properties to their "non-nano" counterparts of the same substance. This is due to three main reasons; size, shape, and functionalization. Take "bucky balls" for example. Bucky Balls come in many different sizes but most commonly are about 1 nm in diameter, with a molecular formula of C_{60}. Molecules of this shape and size allow for other smaller molecules to be enclosed inside the hollow ball. “The ‘buckyball’, being the roundest of round molecules, is also quite resistant to high speed collisions.” (Narinder Kaur, K. Dharamvir and V. K. Jindal, Dept. of physics, Panjab University Chandigarh). The strong Carbon-Carbon bonds throughout the structure laid out in the structurally sound sphere that resembles a football mean that the “bucky ball” has an incredibly high tensile strength. Functionalized bucky balls are gradually being developed and functionalized colloidal gold has already been successfully constructed. This basically means that another atom or group of atoms can be added to the surface of the spherical structure, which would allow the entire nanoparticle to either bind onto another larger molecule e.g. protein, or allow it to react with another molecule so that the hollow shaped ball breaks down structurally. However, nanoparticles also retain many properties, such as the conductivity of pure carbon and the infra red absorbance of many metals.

...AND WHAT’S THIS GOT TO DO WITH MEDICINE?

Nanotechnology within medicine is only beginning to be employed, but it iss rapidly attracting serious interest, both amongst researchers and doctors. Current applications include wound dressings that contain silver nanoparticles which work as a bactericide. Nanofibres capped by a cluster of amino acids have also been shown to prevent scar tissue formation, and in some cases increase the chance of recovery after spinal cord injury when injected near neurons of mice. However, this is barely the beginning, as there are so many nanoparticles with so many intriguing and different properties, there could be many, many more applications within medicine for nanotechnology. In my discussion I am going to propose various new scenarios for applications of nanotechnology focusing on treatment within oncology.

HANG ON A SEC... WHAT ABOUT..?

As with any new technology, there are new background issues that need to be considered. These could range from ethical to social, or environmental to economic, I will briefly allude to these later in the discussion, as medicine importance. For many, these topics could prove to be of greater public interest, than the science behind it all.

DISCUSSION

CANCER

THE FACTS

Cancer is a disease where cells have been caused to grow abnormally and in an uncontrolled manner. This forms a tumour which can then cause the cancer to spread to other parts of the body. If cancer is not detected and treated early enough, it is often fatal. There are over 200 types of cancer, because there are over 200 types of cell. Cancer develops when a mutation has occurred in any oncogenes or tumour suppressor genes (genes involved with the regulation of the cell cycle and cell division) of a cell’s DNA. Mutations can occur by any number of means but most commonly by the reaction of radicals with DNA or the ionisation of DNA. That is why there is no definitive cause for cancer. Radicals are commonly present in many drugs and foods, including tobacco, but they are also formed by many of the body’s normal mechanisms. Ionising radiation can take many forms and low levels of it are quite common, but the most common form of radiation, and that of the largest threat to everyday life, is UV radiation from the sun. A person may also have a genetic predisposition to develop cancer. All of these factors can help to stimulate cancer development, but that is not to say that avoiding these factors will inhibit cancer growth (nor that failing to avoid them will induce it). Cancer has the potential to affect anyone and everyone.

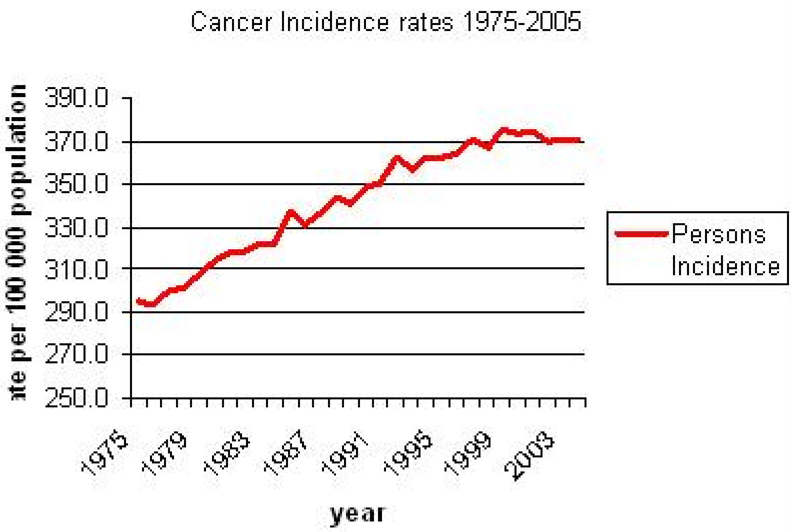


Figure 2

Figure 2 shows the rate of cancer incidence from 1975 to 2005. This shows an obvious increase during the past few decades, which is likely to be because of the change in lifestyles since then, as well as improvement in medical care, leading to longer lives. In the UK, 1 in 3 people will develop cancer in their lifetime. This means that effective treatments are vital for survival rates to maximise.

CURRENT TREATMENTS

The three main treatments for tumour removal are; surgery, radiotherapy, chemotherapy. The appropriate treatment is dependent upon location, size, stage of tumour, as well as circumstance of patient. The optimum aim is to completely remove the tumour. However, the only possible way of doing this is often at the expense of the individual, by these treatments. Surgery is very invasive, and often a patient must undergo various operations before the tumour has been fully removed, and there is still a likely hood of recurrence. Radiotherapy essentially destroys the cells by causing cell death. There are two types of radiotherapy (external and internal). External radiotherapy uses high energy photon beams (X-ray or gamma ray) directed towards the site of the tumour. Internal radiotherapy uses radioactive implants or liquid inserted into site of the tumour to cause cell death of cancerous tissue. However, with both of these therapies, surrounding cells can also be damaged and in drastic cases ionise the DNA of surrounding cells and cause cancerous mutations. Chemotherapy uses cytotoxic (toxic to cells) drugs to destroy a tumour. This targets fast growing cells the most (cancer cells grow very fast). But there are many other body cells that also grow fast, throught the body. The chemotherapy drugs kill these cells too, including digestive cells, blood cells and sex cells. This can cause hair loss, make people feel very sick and tired and more prone to infection and infertility.

POTENTIAL TREATMENTS INVOLOVING NANOTECHNOLOGY

WHATCHA GOT COOKIN'?

Colloidal gold is an aqueous suspension of gold nanoparticles. These gold nanoparticles can range from about 1.5nm to 250nm in size. Naked (non-functionalized) colloidal gold has been shown to have no cytotoxicity and no fatal toxicity to mice. They also have a very large surface area (Figure 3), whilst maintaining a lot of the properties of regular gold e.g. conductivity, low reactivity. These properties for gold mean it is ideal for usage in nanomedicine. But the question is; how do we use it for cancer treatment? Well, one of the best ways

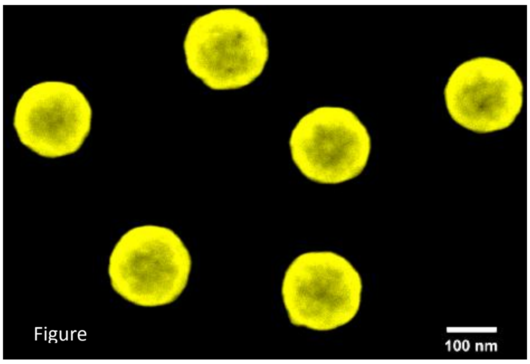


Figure 1

of removing tumours is by effectively 'cooking' them. This means using infra red radiation to heat up the cancerous cells. But directing IR light externally towards internal tumours is very ineffective, and this alone would not destroy cancerous cells. That's where these gold nanoparticles come in. If we functionalize gold nanoparticles with cancer seeking antibodies or proteins, we can cause these nanoparticles to be targeted towards, and taken up by cancerous cells. Then when IR radiation is directed towards the tumor, it is absorbed by the gold nanoparticles (due to their conductivity), where the nanoparticles will then radiate heat directly into cancerous cells, in effect, 'cooking' the tumour till destruction.

Benefits of this treatment include:

- No chance of inducing cancer in surrounding healthy tissue, as infra red radiation is completely non-ionising.
- Minimal side effects, as the destruction of cells is confined to the tumour.
- Completely non-invasive. The Colloidal gold is simply ingested or injected intravenously, because the nanoparticles can pass through the body system without detection by immune system.

Possible disadvantages:

- Functionalized gold nanoparticles have not yet been fully tested for toxicity; there could be some unforeseeable side effects.
- It is still not yet fully known how the body would dispose of colloidal gold. There is plausibility that the nanoparticles will linger for many years after treatment.
- Synthesis of colloidal gold could prove to be very costly, if there is a large demand for it.

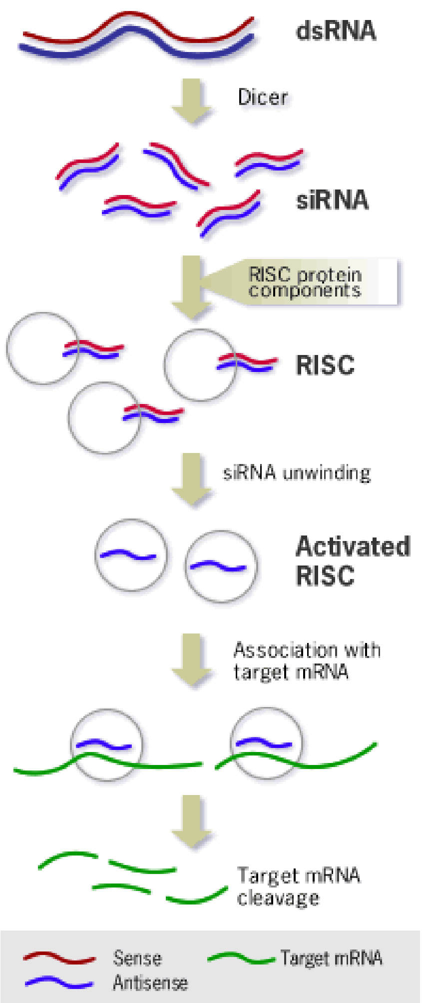


Figure 1

<u>SILENCE!</u>

RNA interference is a cellular mechanism present in many worms, plants and insects. It involves long double stranded RNAs called dsRNA, which, in essence, silence the expression of particular genes (Figure 4). First of all, the dsRNA is broken down in to smaller sections called siRNA. This is done by a Dicer enzyme. The siRNAs assemble themselves into complexes known as RISCs. These RISCs are activated when the siRNAs unwind. The siRNA then acts as a guide for the RISCs, taking them to complimentary mRNA molecules (before they have been translated). Where the RISCs then cleave and destroy the mRNA molecule, rendering it useless for translation. And so the protein for that gene is not synthesized.

This mechanism could be triggered in mammalian cells, meaning we could effectively silence mutated oncogenes. However, introduction of dsRNA prompts an antiviral response. This can be bypassed by simply introducing siRNA, but "if you just inject naked siRNA into the body, it gets broken down within minutes—it has no real stability" (Anil Sood M.D., M.D. Anderson). That means to induce RNAi we need a vehicle to carry siRNA to those desired cells.

Silk fibroin is a protein created by silkworms in the production of silk. It can be reconstructed to form nanoparticles less than 100nm in size. These nanoparticles have many of the same properties as normal fibroin, including biodegragability and non-toxicity. It has also been shown to be completely taken up by cells. Using this information, we can propose that one potential of fibroin naoparticles within nanomedicine, would be to deliver siRNA to desired cells, so as to inhibit translation of mutated oncogenes. This would work, because the fibroin would break down and release the siRNA into cells.

Benefits:

- Fibroin is non-toxic and biodegrades when in vivo, meaning that there are minimal side effects
- This could potentially, not only prevent any further growth of the tumour, but also prevent any recurrence of cancer.
- It is non-invasive and does not require Hospital supervision it can be taken at home, in comfort.

Disadvantages:

- This treatment may not last for very long, so continuous medication may need to be taken. This can be laborious and expensive.
- This would not actually remove tumours, only prevent further growth.
- Targeting particular genes of particular cells can be very hard and may require some sort of targeting system.

FATTIES

Lipids are essential in the human body, and of course, they're non-toxic and degradable. They have no net charge and so are not detected by immune responses at all. Researchers have now developed lipid nanoparticles, with the potential of molecules binding to the surface of these nanoparticles. These could then be used as carriers of cytotoxic drugs used in chemotherapy. This would mean the drugs would not affect healthy tissue, as the nanoparticles could be constructed so as to target the cancerous tissue, and nothing else. The nanoparticles would be taken up by cancerous cells via endocytosis. Inside the cell they could release the cytotoxic drugs and cause the cell and surrounding cells to go under cell death, hence, eliminating the tumour.

Benefits:

- Reduced side effects of chemotherapy, because the drugs would not attack all fast growing cells in the body but only those targeted, i.e. tumours
- Destroys tumour completely so less chance of recurrence
- Non-invasive

Disadvantages

- Difficult to time release of drugs, because lipids have no net charge and are relatively unreactive.
- Fatty acids are broken down in an oxidation process in mitochondria, but reseachers are unsure as to whether these nanoparticles will be able to do the same
- The size of the nanoparticles may limit the amount of the cytotoxic drug that can be carried, and so larger doses may need to be given.

WELL THAT SEEMS GREAT, BUT...

New areas of science and technology require a great deal of attention in regard to social aspects, i.e. environmental, economical, ethical and legislative action. If this new science has a large potential in medicine, the importance of these aspects increases greatly, not least because we must also consider toxicological aspects, within both research and practice. Since health care is such an integral part of modern society, these topics simply sannot be neglected.

HOW SAFE ARE THESE NANOMATERIALS?

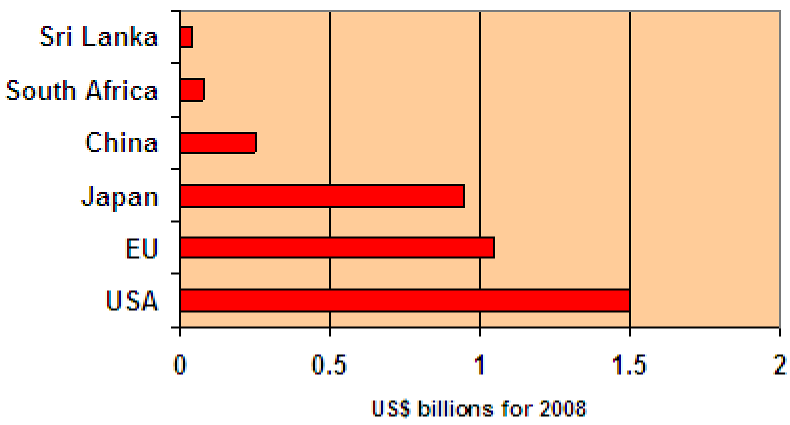
The toxicology of nanoparticles is very important, because it is such a new and unexplored area of science. Not only that, it is difficult to predict how different nanoparticles may react in the human body, both because of the complexity of the human body, and because nanomaterials have such differing properties to regular substances. In vivo and in vitro investigations into toxicology must be carried out, if medical applications of nanotechnology are to be pursued. Many in vivo toxicological tests have been carried out on some nanoparticles, with colloidal gold already getting the green light. Other tests have shown that nanoparticles could be just as harmful as asbestos if inhaled in sufficient quantities, including carbon nanotubes (the suggested poster child of nanotechnology) However, animal testing is not always a true indication of human toxicology. These tests also do not provide any information on side effects. Mice cannot tell us how they are feeling, and we can only really observe fatalities, and that's as far as it goes. Once we have a significant amount of evidence indicating that particular nanomaterials do not cause fatalities in mammals, there must be extensive, unbiased, independent human testing before any nanotechnology can be used in medicine as treatment.

WHAT ABOUT THE ENVIRONMENT?

There are growing concerns as to the environmental impact of nanotechnology. This is because it is such a new technology that we are still not sure of how it decomposes. Are we going to have another environmental crisis similar to the current issue of plastics disposal? Scientists have very little understanding of whether nanomaterials are biodegradable or not, because these kind of materials do not occur in nature at all. Some studies have actually shown they may inhibit biodegradation. When silver nanoparticles are released into the environment, they stop the growth of bacteria vital for organic decomposition, and this could have serious consequences for wildlife and possibly even agriculture.

AND THE GLOBAL ECONOMY?

For most western nations medical care makes up substantial part of the economy, including the large number of those employed by medical institutions, the cost of private medical care, and of course the vast quantity of money gained by pharmaceutical companies. However for less developed nations, it takes up a much smaller part of their economies. This of course means less medical treatment for the general public, which in turn affects the interest of pharamaceutical companies, and so diminishes the availability of new and progressive treatments. Nanomedicine is no exception. Let's look at the amount of money spent on nanotechnology research (Figure 5). The graph clearly shows that the nations with the greatest wealth are spending the most on nanotechnology. Does this mean that only these nations will benefit from the new discoveries that nanotechnology will bring to medicine? It seems so. And this is because fabrication of nanoparticles is costly. These are intricate processes which require hi-tech equipment, and poorer nations don't have access to this. But is it right to inadvertently deny better medical treatments to the populations of



poorer nations? This should be a subject of international discussion. I suspect that it will be very difficult to come to a unanimous decision. I believe that these new technologies should not be seen in any way as an opportunity to make money. Instead they should be viewed as medical treatment accessible to those in most need, regardless of their nation's political or economic circumstance.

I'M STILL A BIT SUSPICOUS...

As nanotechnology is such a new area of science, there is generally little public understanding of it. People may have heard of the term, but its uses, its benefits, and its dangers are little known. For these technologies to be used in a proficient manner within public medical care, there must be an emphasis on nanotechnology education. Members of the public (and more importantly patients) must be fully aware of both benefits and risks of nanomedicine treatment. This will allow them to make an informed decision as to whether they wish to accept or deny treatment. Education of this kind will also minimise any speculative fears and accusations around nanotechnology, as information will be ready available and any new research, especially if publicly funded, should be as transparent as possible.

COULDN'T THIS ALL GET A BIT OUT OF HAND?

The best way to impose these standards would be by implementing regulations and legislative action, both nationally and internationally. At the moment there is very little regulation, as there is significant debate as to who should be in charge of overseeing these regulations. This has therefore led to comparisons with 'mad cow' disease, thalidomide and GM foods. This of course, does not help with the public perception of nanotechnology. In order for nanotechnology applications to be pursued in new areas of science, especially medicine, laws must be set out, similar to those on stem cell research or new drugs/medical devices, with legal action upon any breach of these laws.

CONCLUSION

HANG ON! IS ALL THIS TROUBLE WORTH IT?!

Yes. Nanotechnology is a totally new and untapped resource for exploration. This kind of technology can be manipulated so as to gain brilliant applications for all the sciences, not just in medicine. But for medicine these possibilities appear endless (and this is just for the nanomaterials we know of now). New fabrication methods and investigations are being carried out all the time and we could yet find more nanomaterials to work with within medicine. We're only just beginning to unveil the unpredictable and useful properties of nanomaterials, and these too could provide us with better insights into how to develop more efficient diagnostic and treatment methods, especially in cancer. Cancer incidence is on the up, and with life expectancy increasing, and current lifestyles, this is set to rise further. The current treatments for cancer are relatively effective in maintaining moderate survival rates, but they also have many disadvantages, disadvantages that could potentially be avoided using the nanotechnologies that are slowly emerging. Cooking tumours, RNAi, and new drug delivery systems are only the initial possibilities for cancer treatment involving nanotechnology. These technologies are in their early stages; more is yet to come. But it is also important not to expect too much of nanomedicine. As with any new technology, there are drawbacks, drawbacks that cannot be prevented. We must consider all of the shortcomings as factors when using nanotechnology. We, both as patients and medical professionals, must be able to judge for ourselves whether the benefit outweighs the risk, and this will be different for every circumstance. The only viable way of doing this is by informing those that will be exposed to nanotechnology, of all of the surrounding issues I have discussed. By explaining toxicological, environmental, economic and ethical aspects of nanomedicine, an informed decision can be about treatment, by the patients and medical professionals themselves. But perhaps more importantly, both for application and research, both nationally and internationally, strict guidelines for the uses of nanotechnology must be set out, especially in medicine. This will not only help regulate efficient use within hospitals, etc. but also comfort the general population by allowing for discussion and debate surrounding what these technologies should and shouldn't be used for.

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