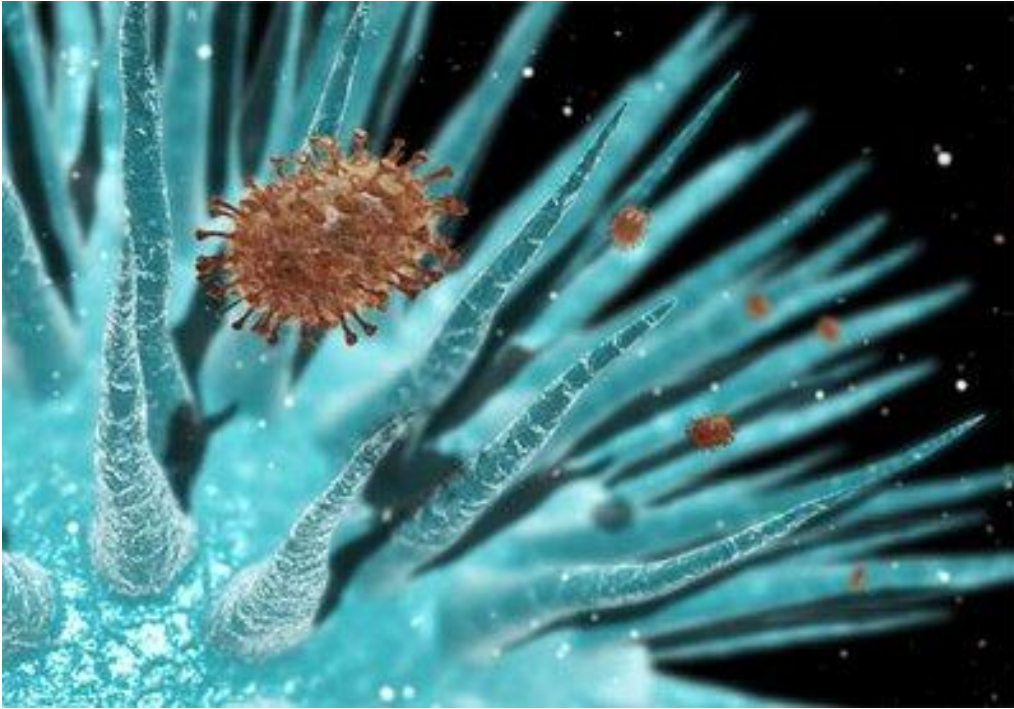


**The Development of Nanotechnology and
its Potential to Revolutionise Drug Delivery
and Key Treatments**



By

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PASS

RESEARCH PAPER
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ABSTRACT

In this research paper I intend to discuss the potential for nanotechnology developments which are striving to help deal with problems that arise in drug delivery and alternative cures for some ailments. People see nanotechnology as the future of modern medicine and in this paper I intend to show how far nanotechnology has come already in supplying key treatments to some well known diseases such as diabetes and cancer.

INTRODUCTION

The Encyclopaedia Britannica defines nanotechnology as “the Manipulation of atoms, molecules, and materials to form structures on the scale of nanometres (billionths of a metre).” Nanotechnology is seen as a relatively recent scientific breakthrough with large margins of potential for development. In fact the origins of nanotechnology date back to 1959, to a talk given by physicist Richard Feynman at an American Physical Society meeting at the California Institute of Technology (Caltech). Here he discussed the concept of single atom manipulation and, by use of tools on such a small scale, that the laws of physics would have different effects. For example, gravity would be seen to take less of an effect while the intermolecular Van der Waal forces will have a much more prominent effect. This theory was seen as physically sound for the time, yet seemingly difficult for the technology of the time to achieve.

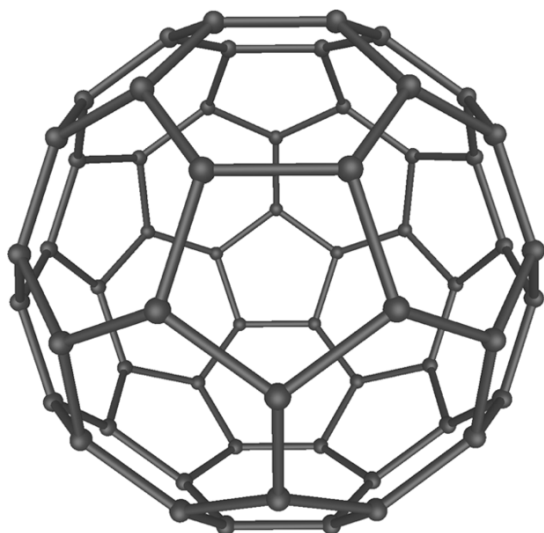


Figure 1 - A C-60 buckminster fullerene ball or 'bucky ball'

It would take another 20 years before the next large step in work with nanotechnology occurred, with the use of the scanning tunneling microscope and the advancement of cluster science, which both in turn led to the discovery in 1985 of the Fullerenes. The Fullerenes are molecules made up of only carbon atoms and are formed into shapes such as spheres (see figure 1) or tubes. The structure of fullerenes is often compared to that of graphite (an allotrope of carbon), yet the fullerenes are classed as separate allotropes.

Diseases such as diabetes and cancer under the monitoring of modern medicine are seen as manageable with correct treatments, whether it be injections of insulin or cycles of chemotherapy. These kinds of treatment are not only a large inconvenience, but also can be a threat to life as chemotherapy is a drug that can't be completely localized and can take serious strains on the human body (due to its toxicity). The belief here is that by using nanoparticles the methods of drug delivery can be changed to become, not only more effective, but also safer for patients.

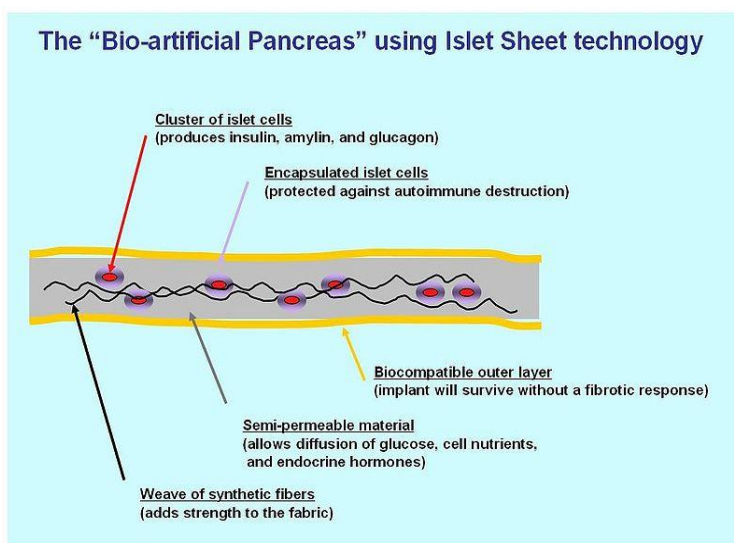
DISCUSSION

Diabetes

Diabetes is a disease which causes the pancreas to stop producing insulin, which is important for controlling blood sugar levels. To help maintain homeostatic sugar levels diabetics must take regular doses of insulin, which is injected directly into the bloodstream. This is not only a real inconvenience of having to constantly monitor blood sugar levels but also can have health risks in that poor circulation to limbs can potentially lead to the loss of said limbs.

How Nanotechnology can help

“Insulin injections may soon be a thing of the past for diabetics thanks to nano-technology”.



At UCSF Professor of Bioengineering, Tejal Desai, has developed a new piece of nanotechnology which would contain millions of pancreatic cells that secrete insulin. These would be contained in tiny capsules that can be implanted into the body in an effort to create an “artificial pancreas”. When blood sugar flows inside the capsule, it stimulates the cells to produce insulin to control sugar levels. The device has nano pores; pores so small that the body's antibodies cannot get in to attack the cells, but large enough that the insulin can flow out and into the body.

Figure 2 - a diagram of a potential “bio-artificial Pancreas” engineered with nanotechnology.

The overall idea of the engineered pancreas is to ensure a constant delivery of insulin to a diabetic without the need for injections and rarely the need for sugar monitoring. The concept of how this could work relies on the principle of diffusion (working with the concentration gradient). With the simple biological notion that should there be a lower insulin level in the body than the newly produced insulin from inside the artificial pancreas; the artificial pancreas will be able to transfer into the body acting as if it were a real pancreas. This is achieved by a partially permeable membrane which is able to control the amount that is let out, which is exactly what is wanted from an artificial pancreas. There are some issues that need to be addressed, first is that any form of artificial being found in the body will most probably be recognized as a foreign aspect and most of the time the body will attack the ‘foreign body’ which can often cause damage and cause severe illness (such as an overdose on insulin resulting in a heart attack). How scientists are getting around this is that the outside of the implant will be made up of a bio compatible outer layer, this will help ensure that the implant is not attacked by the body in a fibrotic response. This outer layer needs to be made up of thin hairs which allow other bodily cells to pass over it, without detecting the pancreas. A suggested idea was that gold be used (due to its property of being body friendly) but this does have its own problems in that too much may cause metal poisoning and also cost wise; gold is a limited resource so it would not be a wise move to base a potential treatment for diabetes on a scarce commodity.

Cancer

Cancer is a well-known disease due to its coverage in the media and worldwide fund raising initiatives. "In 2007 cancer caused about 13% of all human deaths worldwide (7.9 million)." Cancer is a class of disease which sees the rapid buildup of a group of cells, in which the cells display abnormally fast growth rates; these rapidly growing cells intrude on other tissues in the body. The current treatment of cancer is either chemotherapy or radio therapy. Chemotherapy is the treatment of cancer by using a powerful toxin which kills off the cells. The problem here, however, is that it is hard to localize the toxin exactly and side effects occur such as loss of hair and patients feeling weaker afterwards. Radiotherapy is the use of radio waves on the exact area. This is expensive, time consuming and for the number of cancer patients in the world, isn't very effective in treating the maximum number of patients. Rates of incidence are rising as more people live to an old age and lifestyle changes that are occurring in the developing world, so with a rising number of cancer patients there's a need to find a sustainable method of treating cancer which is accessible and useable by all people.

How Nanotechnology can help

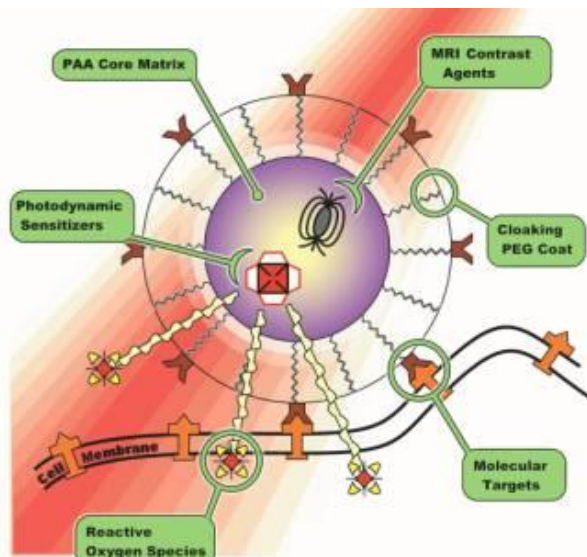


Figure 3 - A diagram designed by scientists at MIT in Boston for a nanotechnology based 'smart bomb'. A non invasive method for treating malignant tumours.

The most common idea to have been developed from research into cancer fighting nanotechnology is the idea of the named 'smart bomb'. Research from the Massachusetts Institute of Technology (MIT) in Boston has been conducted to come across a new design (published in the 2005 journal Nature) seen in figure 3. The idea of this technology is that the nanoparticles will protect medicinal doses of chemotherapy in the inner core, with an outer core consisting of specialised chemicals which allow it to transfer through a body without being attacked.

The Nano particles are of a size where they can transfer through normal vessels safely but also won't transfer through tumour vessels so they know where to release their chemicals.

A quote from the researchers at MIT on the new treatment; *"This therapy has many benefits over standard chemo and radiation therapy. Patients are less likely to suffer nausea, vomiting, hair loss and other side effects. Also, when tested on mice, the mice using this therapy lived longer than their counterparts on traditional chemo and radiation therapies."*

A quote from angiogenesis pioneer researcher Judah Folkman, of the Children's Hospital Boston said *"It's an elegant technique for attacking the two compartments of a tumour, its vascular system and the cancer cells,"*. So it appears that the use of nanotechnology for treatment of cancer is appearing to be a way forward.

Of course this isn't the only way scientists have been developing nanotechnology to help treatments of cancer. Dr Hongjie Dai from Stanford University, after admitting *"One of the longstanding problems in medicine is how to cure cancer without harming normal body tissue."*

Sometimes the problem is that even with precise placement the drugs themselves are the problem, so it can be important to research how nanotechnology can cure disease by other, more unorthodox, methods.

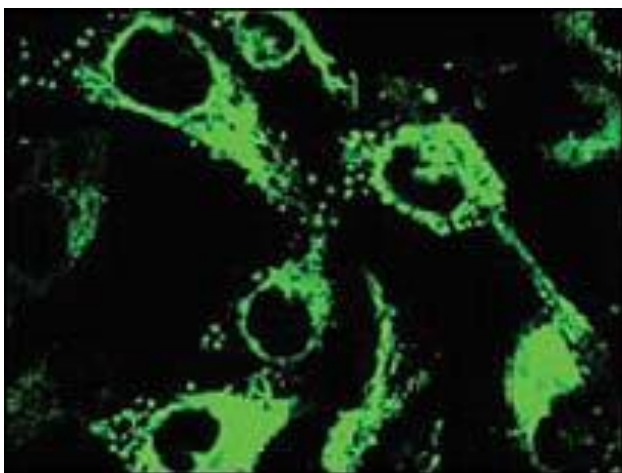


Figure 4 - The fluorescent parts show where tubes have been inserted.

After realising a problem he set out to develop a new method of treatment for cancer cells. This new method that has been developed is different from other uses of nanotechnology. This treatment is done by inserting microscopic, nanotechnology engineered, carbon nanotubes into malignant cancer cells. These tubules are then exposed to near infra-red radiation, which as a result heats up the rods and kills the cancerous cells. The process works by placing a solution of carbon nanotubes under a near-infra red laser beam, the solution heated up to about 70C in two minutes. They then placed the tubules inside cells, and found they were quickly destroyed by the heat generated by the laser beam.

One of the biggest developments in this method was to ensure that only targeted cells would be treated and all the healthy cells would be unharmed. The researchers did this by taking advantage of the fact that, unlike normal cells, the surface of cancer cells is covered with receptors for a vitamin known as folate. The nanotubes were coated with folate molecules, which make it easier for them to pass into cancer cells but also making it so that it is impossible for the tubules to bind to any healthy cells. Once exposed to the laser, the tubules are able to kill off all the diseased cells but leave the healthy cells unharmed.

Even with this original development into the use of nanotechnology, it is still however important to note that this technique may still need some refining first before any form of clinical based use could occur. An example is potentially attaching an antibody to a nanotubule to target a particular kind of cancer cell, which in theory could reduce the damage that occurs to the body further and may also serve as a method of keeping the cancer away. One of the main problems with treatment of cancer is that if not all the malignant cells are disposed, with a suitable margin of safety, then there is a chance that the cancer may return and in some cases may be more violent than previous treatments. *Dr Emma Knight, of the charity Cancer Research UK, said: "Nanotechnology has a lot to offer biomedical science, and the results of this paper suggest yet another way in which it may help in the fight against cancer. However, this work is still at a very early stage. The researchers have shown that near-infra red light can cause nanotubes to produce heat that can kill cancer cells. But their work so far has focused on cells that have been grown in culture in the laboratory. Further research will be crucial to see whether these effects can be reproduced in the more complex environment of a tumour and, ultimately, the human body."*

Heart Disease

Coronary Heart disease is when the coronary arteries are found to have lots of arthromeres in them. As a result the coronary artery is seen to be partially blocked up, this restricts blood flow to the heart. A reduction in blood flow reduces the amount of oxygen an area of the hearts gets; this is known to cause pains (known as an angina) or even a heart attack. Plaque build-up, known as atherosclerosis, is the leading cause of these heart attacks and can even cause a stroke. *“According to the American Heart Association, 831,272 people died in the United States in 2006 because of heart disease. That adds up to about one in three deaths.”*

How Nanotechnology can help

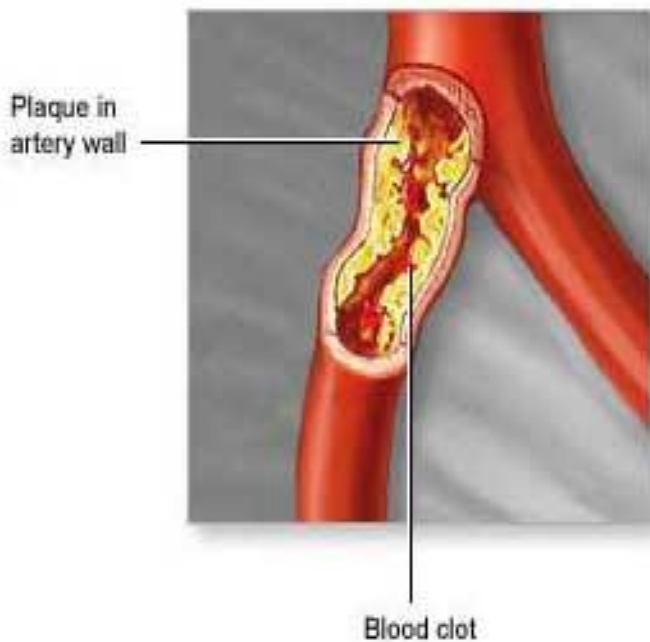


Figure 5 – An example of an artheroma beginning to build up due to large amounts of plaque lining the artery.

The universities researchers at both Harvard Medical School and MIT have built a type of nanoparticle which is able to cling to artery walls and slowly over a period of time release medicine contained inside them. This new technology has been nicknamed “nanoburrs.” The researchers behind this use of nanotechnology say that *“we’re hoping the nanoburrs can offer an alternative to surgically implanting arterial stents that, over time, release drugs to treat or prevent plaque build up on artery walls.”* The main goal of this nanotechnology use is, in order to prevent heart attacks, is to prevent one of the leading causes of heart attacks atherosclerosis (plaque build up). The nanoburrs are designed to target a specific part of the artery called the basement membrane. The membrane is a lining in the arterial wall but is only exposed when the

artery is damaged. Because of this, the nanoburrs can be designed to only go after these exposed areas, which are the damaged areas.

There have been other ideas stemming from nanotechnology which are designed to deal with ailments or issues surrounding heart disease. One new use of nanotechnology is the use of using carbon tubes to create artificial arteries. These artificial arteries could be used in transplants by removing damaged arteries and replacing them with these artificial ones, which in theory could be purposefully designed to ensure that people shouldn’t suffer from atherosclerosis again. These artificial arteries can be engineered from polymer materials, which are combined with nanotechnology based materials, meaning that size can be maximised in order to simulate the same properties as an actual artery. There has however been a listed problem that comes from any form of nanotechnology based implant which would be involved in blood transport, and this is that these replacements can’t pulse as properly as a real artery. This problem has been noted to exist even more prominently in smaller sized fits (which defeats the objective of nanotechnology), the problem with ineffective pulsing is that these implants can then lead to clots if they’re unable to cope with the blood pressure. The solution that was introduced to meet this problem, is that by mixing the polymers with the nanomaterials, it is hoped that this will create a much more flexible substance which could handle the job better.

Ethics of Nanotechnology

Problems- *“Production of carbon nano products totalled about 710 tons in 2010, for a rough value of \$435M, calculates Innovative Research and Products Inc. (iRAP). The company predicts that this will swell to 9,300t and \$1.3B by 2015.”*

The price of research into nanotechnology is very high so that it is majority governmental organisations which control the research of nanotechnology. So the question to be answered here is ‘how can everyone’s separate needs for research into different fields of nanotechnology be met if you have a government driven agenda?’ i.e. will they choose to prioritise the use of nanotechnology in medicine over its use in other fields like architecture, or will potential military uses be seen as the governments main agenda. Other political issues to be considered; should a problem arise from the use of nanotechnology, who should be held accountable? An example could be; if the artificial pancreas passes clinical trials and is accepted as a treatment, if a patient dies as a result of receiving this treatment then who could be held accountable for the problem? Would it be the doctor who prescribed/administered the treatment, the persons who allowed it to pass clinical trial stages, the engineers who designed and built the technology or even the supplier of materials (such as large amounts of carbon) for supplying faulty materials. The point of this example is to show that in the event of a problem occurring with the technology, once it’s out in the world as an accepted method of treatment, the sheer number of different people involved in nanotechnology would make it hard to hold anyone accountable.

Ethical issues also arise from the development of nanotechnology; one example is the argument over the sharing of the technology. The research, development and application of nanotechnology is a costly and timely procedure that can only realistically happen in the richest counties of the world. As a result of this, the governments of these countries may believe that they are entitled to keep the technology exclusively to themselves, which would deny many much poorer countries any chance of benefiting from it. When the technology in debate is medicinal nanotechnology, then who should truly be allowed to deny other people the chance of living a better and more importantly healthier life. Nanotechnology is seen as a revolution in technology with many possibilities, and while my paper is focused on the potential for medicinal advancements, it is important to point out that mentioned uses of nanotechnology in the future could lead to developments in nanotechnology being weaponized. That’s why a large issue that may need to be addressed is, as research into nanotechnology deepens, who will police this research or more significantly what will be the limits for the research? As mentioned above, it’s the governments of rich MEDC countries which are controlling the research and, if they want to see military uses as a priority, then who would be likely to stop them?

A list of Stakeholders

- The Government - since it funds much of the nanotechnology research
- DARPA - enforcing ethical guidelines may conflict with military research
- Researchers - their freedom of how to conduct their research and what to conduct their research on
- Explicit users of nanotechnology - may slow down development of the technology
- Potentially Everyone - nanotechnology may eventually be so far reaching, it could affect everyone

CONCLUSION

While doing my research, one issue I found that came up time and time again was one which I feel should be rather an obvious and basic idea but however surprisingly few references mentioned. It was the idea of what would happen to the nanoparticles used in certain aforementioned treatments, (the main example being drug delivery for cancer and coronary heart disease). One site gives a possibility that can be used to answer the question. The solution is that you would create biodegradable nanoparticle composed of PGLA (poly D,L-lactide-co-glycolide). This compound has been tested at sustained and more localised delivery for a variety of different agents and these include plasmid DNA, peptides, proteins and other low weight molecular compounds. Research that followed on from this, was based around the mechanism of intracellular uptake of these PGLA nanoparticles. The idea behind the research was to see how the nanoparticles were trafficked and sorted into different cellular structures. The main goal was to see how therapeutically efficient the body would be at sorting these particles. The results from this experiment were that there was a rapid escape of PGLA from the endo-lysosomal compartment into cytosol following their uptake. With this research there is now an answer to my initial issue, in that there are methods that researchers can use in order to ensure stability of nanoparticles in the body. Other methods that have been outlined is the idea of particles which are covered in proteins with hairs on them, so that they can past by other cells such as lymphocytes which are programmed to remove foreign bodies along with antibodies which serve the same purpose.

In my view, nanotechnology developments mean that it seems the main question now is not if nanotechnology can ever become a legitimate treatment but more when will it reach the point that doctors, researchers and more importantly patients are happy to use it as a recognised form of treatment. It seems that nanotechnology developments, such as the nanoparticle, are definitely a way forward in treating certain diseases, which have before now been a problem for doctors worldwide. There are some negatives in the use of nanotechnology, which were previously mentioned, but I believe that they could be large halting factors in the use of nanotechnology as a medicinal treatment. The main reason against nanotechnology is that these small machines, which are put inside a patients body are engineered by people other than doctors. Therefore, should there be a problem with the relatively new science, then who would be able to fix the problem easier, doctors or bioengineers? However, with these issues it is important to note that these aforementioned developments in nanotechnology are truly unique and could arguably save many lives with safer drug delivery along with better treatments, so in my personal opinion it is worth continuing the trials and research into nanotechnology so that people may find in a few years time there will be less dangerous treatments to very common diseases. While nanotechnology can revolutionise drug delivery, I also believe that there are other uses to nanotechnology which can help cure diseases, as sometimes it's the drugs themselves which can cause the damage (chemotherapy as the main example). So that is the reason why I mention the use of nanotubules, as while it may not be so much a drug delivery, it is delivering a version of a cure for an infamous disease with a reputation for being difficult to treat.

So for these reasons I believe that nanotechnology does have the potential to revolutionise the delivery of drugs in some very common diseases in today's society.

REFERENCES

www.smartplanet.com/people/video/...to...insulin.../370926/ -To end injections for diabetics

<http://www.bestsyndication.com/2005/Dan-WILSON/Health/072805-nano-technology-cancer-treatment.htm> - Nanotechnology used to kill cancer cells

<http://news.bbc.co.uk/1/hi/health/4734507.stm> -Nanotechnology kills cancer cells

http://www.computerworld.com/s/article/9146078/Scientists_use_nanotech_to_prevent_heart_disease -Scientists use nanotechnology to help prevent disease

http://www.electroiq.com/index/display/nanotech-article-display/2122701767/articles/small-times/nanotechmems/materials/carbon-nanotubes/2011/2/report_nanocarbon.html.- Materials of nanotechnology

<http://www.scu.edu/ethics/publications/submitted/chen/nanotechnology.html> -The ethics of nanotechnology

<http://www.nano-biology.net/showabstract.php?pmid=12628320> -A collection of nanotechnology resources

<http://www.online-diabetes-information.com/introduction-to-diabetes/using-nanotechnology-in-diabetes/> - Nanotechnology and diabetes

<http://mritechnicianschools.net/2010/25-ways-nanotechnology-is-revolutionalizing-medicine/> - Ways nanotechnology is revolutionising medicine