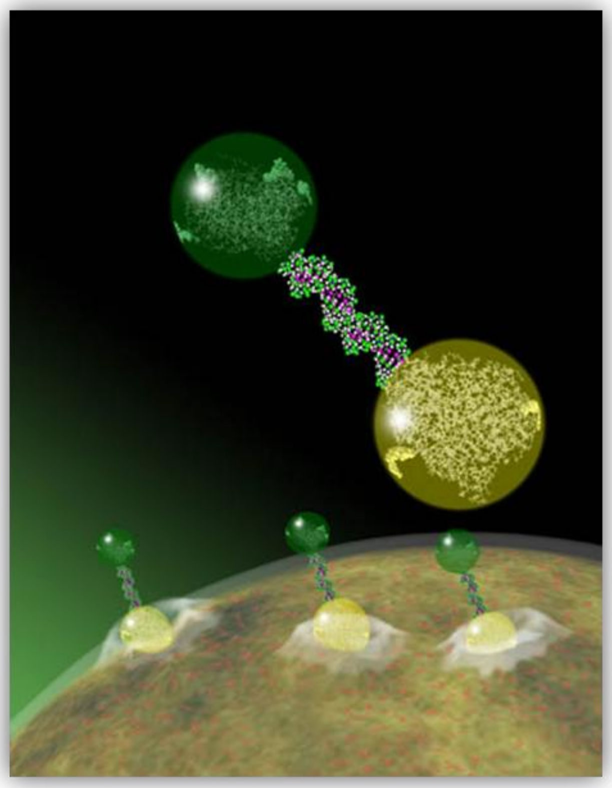
The Potential Role of Nanotechnology in Cancer Therapy



By David Rassam
And
Shiv Sharma
PASS

Research Paper
Based On
Pathology Lectures
At Medlink 2010

Abstract:

Nanotechnology is a multidisciplinary field which combines engineering, biology, physics and chemistry. This field has evolved over the past half century and most scientists now agree that it has truly come of age. Nanotechnology is well placed in the diagnosis and treatment of cancer as it enables doctors and scientists to operate at a molecular and cellular level. This allows treatment to be focussed on specific areas without impacting surrounding organs and systems. Using nanotechnology, it is possible that cancer cells could be targeted and destroyed with almost no damage to surrounding healthy tissue. The purpose of this paper is to investigate the developments and future uses of nanotechnology in diagnosing and treating cancer. In addition, we will explain how the advances in the uses of nanotechnology, combined with other developments in medicine, have led scientists to predict that cancer will be eradicated in less than ten years.

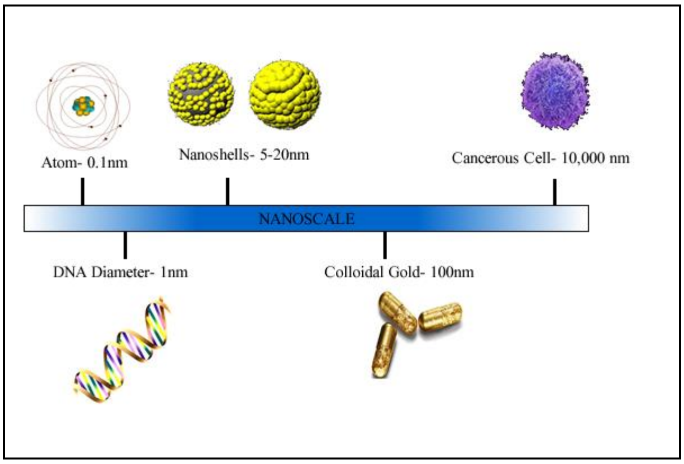
Intro:

"I want to build a billion tiny factories, models of each other, which are manufacturing simultaneously. The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big. — Richard Feynman, Nobel Prize winner in physics" [1]

The concept of nanotechnology began in 1959, when Richard Feynman first proposed the principle that devices and materials could one day be constructed to atomic detailing. In his reputable speech "There's plenty of room at the bottom" he addresses the problem of controlling and manipulating objects on a miniscule scale [2]. His thoughts and hypothesis were the grounding for what was and is the nano- revolution.

Nanotechnology deals with structures that are of 100 nanometres or smaller. The majority of animal cells are approximately 7,000 to 20,000 nanometres in width. Therefore, it would be ideal for nano tools to be used to interact with the structures within a cell such as the DNA and proteins. The following diagram illustrates the relative sizes of nano particles [3]

FIGURE 1



Materials reduced to the nanoscale can show different properties compared to what they exhibit on a macroscale, enabling unique applications. A material such as gold for example, which is chemically inert at normal scales, can become a potent chemical catalyst at nanoscales. Much of the interest in nanotechnology stems from such quantum and surface phenomena that matter exhibits at the nanoscale.

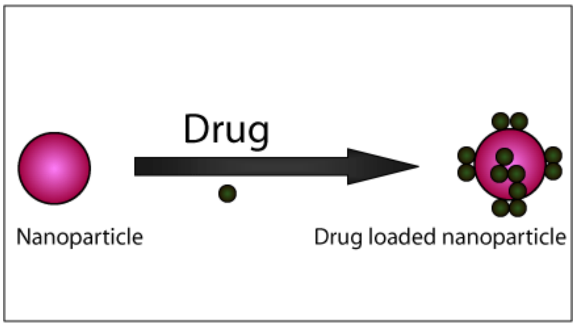
After Richard Feynman's observation, many scientists came out with novel ideas to develop new devices at the atomic level. Gordon Moore, for example established that silicon transistors experienced a constant process of downward scaling which we now call Moore's law. He commented that the number of transistors that can be placed inexpensively on a combined circuit has doubled roughly every two years. [4]Many technologies that descended from conventional solid-state silicon methods for fabricating microprocessors are now capable of creating features smaller than 100 nm, falling under the definition of nanotechnology. It is generally believed that future nanosystems will be hybrids of silicon technology and biological molecular machines. It is to be noted that the emergence of nanoparticles has been underpinned by complementary technologies such as nano microscopes and nanolathes for constructing molecular machines.

Current research and Medical Uses of Nanotechnology

Drug Delivery

One of the most important applications of nanotechnology in medicine which is currently being tested involves employing nanoparticles to deliver drugs or other substances to specific types of cells, in particular to cancer cells. Particles are engineered so that they are attracted to diseased cells, which then allow direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease.

FIGURE 2



One treatment involves targeted chemotherapy that delivers a tumour-killing agent called tumour necrosis factor alpha (TNF) to cancer tumours. One of the major flaws of our body's immune system is that is "oversensitive". It will attack almost anything foreign that enters our body. TNF is attached to a gold nanoparticle along with a chemical (Thiol-derivatised polyethylene glycol) which "hides" the TNF possessing nanoparticle from our immune system. This method to deliver TNF and other chemotherapy drugs to cancer tumours is called cytimmune.

An alternative approach uses nanoparticles constructed from carbon. The value of nanoparticles made of diamond is multifaceted. Very recent studies report that tiny flecks of carbon can shrink tumours in mice by delivering chemotherapy drugs to cancer cells. Made of carbon, they're non-toxic, and the body's immune system doesn't attack them. They can bind tightly to a variety of molecules and deliver them right into a tumour. And because they are only 2 to 8 nanometres in diameter, they are easy for the kidneys to clear from the body before they block up blood vessels, a long-standing problem in nanoparticle therapy.

To study the use of nanodiamonds' in cancer treatment, doxorubicin, a standard chemotherapy drug, was injected into mice with drug-resistant breast and liver cancer. With the help of the diamonds, the drug stayed in the bloodstream 10 times longer than usual, making it much more effective. As a result, the tumours shrank significantly, as reported in Science Translational Medicine.

This technique also decreased the toxicity of the drug. The researchers were able to inject the mice with doses of doxorubicin that normally would be lethal. But the drug stayed bound to the diamond until it reached the tumour, so it didn't damage cells elsewhere in the body, and the animals survived.

It was also interesting to note that the livers of the mice didn't increase enzymatic activity as they normally would in response to high levels of a toxic substance. Most importantly, the doxorubicin-decorated diamonds had no effect on white blood cell count, an indicator of immune system activation that's often the deciding factor in whether a patient can continue chemotherapy.

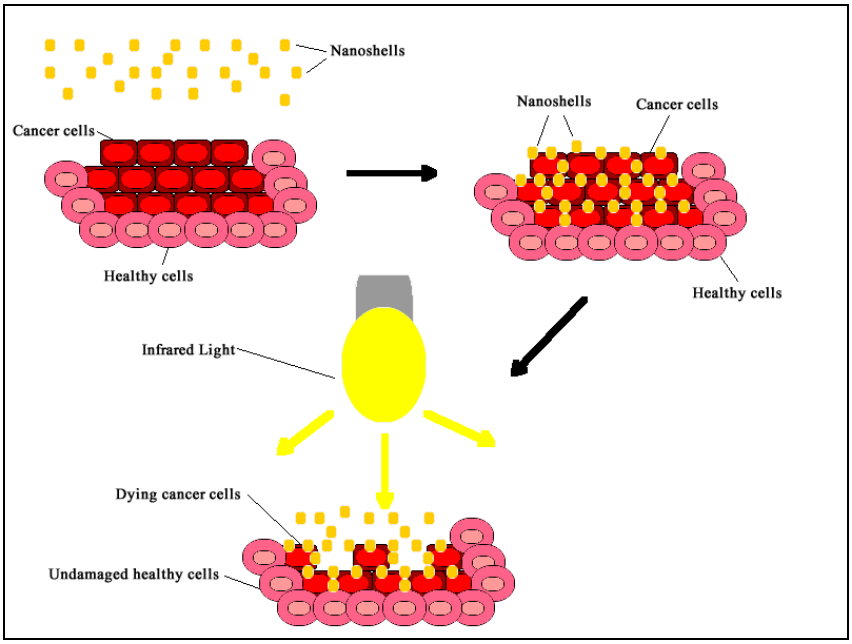
Gene Therapy

Gene delivery is another area of current interest; genetic materials (DNA, RNA) have been used as molecular medicine and are delivered to specific cell types to either inhibit some undesirable gene expression or express therapeutic proteins. To date, the majority of gene therapy systems are based on viral vectors delivered by injection to the sites where the therapeutic effect is desired. Viral vectors can have potentially dangerous side effects due to unintended integration of the viral DNA into the host genome, which can potentially affect the expression of essential genes. Gene therapy using nanotechnology does not suffer from this disadvantage.

Therapeutic Medicine

The use of infra-red light to target heat on to cancer cells has been well documented. Thus the use of nanoshells to concentrate the heat from infrared light to destroy cancer cells with minimal damage to surrounding healthy cells is likely to prove to be very useful in the near future. The following diagram illustrates the use of nanoshells in cancer therapy.

FIGURE 3



In a similar manner nanoparticles which can be activated by x-rays can be used to generate particles that can cause the destruction of cancer cells to which they have attached themselves. This is a much more focussed approach to radiotherapy than is in use today. [5]

A combined chemo-heat therapy method uses not only one nanoparticle to combat a tumour, but two. One nanoparticle is used to deliver the chemotherapy drug and a different nanoparticle is used to guide the drug carrier to the tumour. The guiding nanoparticle would work almost like a magnet, the chemotherapy drug being the metal.

The drug would be able to effectively migrate through attraction to the target. The first step in this treatment involves circulating gold nanorods through the bloodstream. The growing tumour ruptures blood vessels, resulting in the vessels leaking. The gold nanorods exit where

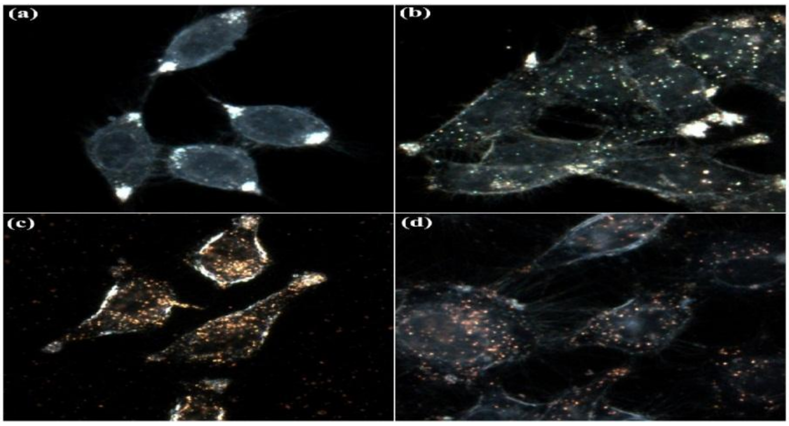


FIGURE 4

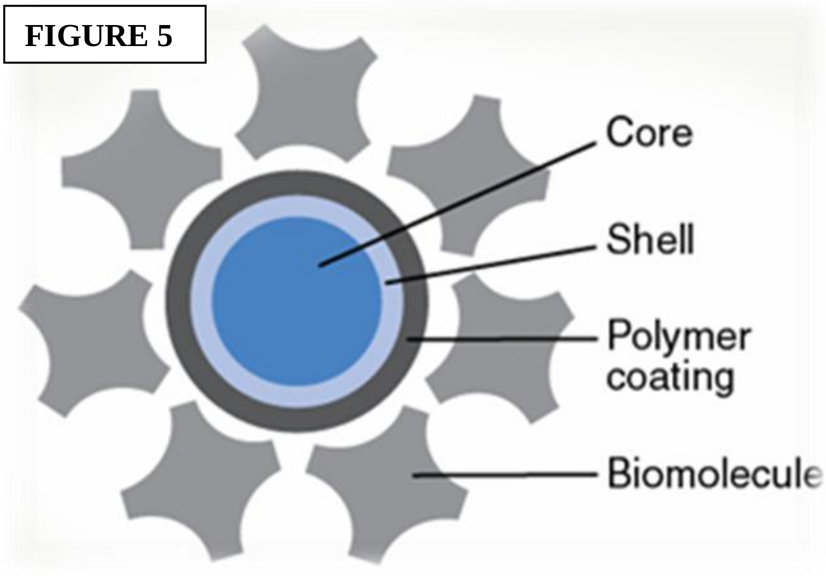
the blood vessels are leaking and accumulate at the site of the tumour. (Shown in sections **(b)**, **(c)** and **(d)**)Once the nanorods gather at the tumour, in this case the pancreas, they are used to concentrate the heat from infrared light (which is generated from a laser outside of the patient’s body); heating up the tumour. This heat stimulates the release of a stress related protein on the surface of the tumour. The drug carrying nanoparticle attaches to the specific amino acids that bind to this protein, so the increased level of protein at the tumour speeds up the accumulation of the chemotherapy drug. This method if put into practise would be suitable for treating most cancers, even those which are deeper in the body.

Diagnostic and Imaging

Nanomaterials are sensitive chemical and biological sensors. They can be integrated into other technologies such as lab-on-a-chip to facilitate molecular diagnostics. Their applications include detection of microorganisms in various samples, monitoring of metabolites in body fluids and detection of tissue pathology such as cancer. Numerous nanodevices and nanosystems for sequencing single molecules of DNA are also feasible.

Quantum Dots® (qdots) are nanoparticles that absorb photons of light, then re-emit photons at a different wavelength and can be used in order to search for cancer tumours in the body. However, they exhibit some important differences as compared to traditional fluorophores such as organic fluorescent dyes and naturally fluorescent proteins. Qdot nanocrystals are nanometre-scale (roughly protein-sized) atom clusters, containing from a few hundred to a few thousand atoms of a semiconductor material (cadmium mixed with selenium or tellurium), which has been coated with an additional semiconductor shell (zinc sulphide) to improve the optical properties of the material. These particles fluoresce in a completely different way than do traditional fluorophores. These Qdots may be used in the future to locate cancer tumours and in the short term in performing diagnostic tests.

FIGURE 5



The use of iron oxide nanoparticles to improve MRI images of cancer tumours has also been documented. The nanoparticle is coated with a peptide (polymer coating) that binds to a cancer tumour; once the nanoparticles are attached to the tumour the magnetic property of the iron oxide enhances the images from the Magnetic Resonance Imagining scan.

Nanoparticles can also attach to proteins or other molecules, allowing detection of disease indicators in a lab sample at a very early stage. There are several areas of research into nanoparticle disease detection systems. One system uses coated gold nanoparticles for diagnostic purposes.

Discussion:

In cancer treatment, doctors are hoping to use the microscopic size of nanoparticles to transport drugs, stimulate a more effective immune response and even combat cancers by themselves. The following section of our research paper details the possible future developments of nanotechnology and its impact on the fight against cancer.

Nanoscale Metals

Experiments on the metal, platinum, in the early 1970's showed that a simple platinum based compound prevented bacteria from reproducing ordinarily. Further research determined that similar effects are seen when tumours are exposed to the platinum compounds. The main disadvantage with platinum cancer therapy is that it has a high toxicity, which results in healthy tissue being damaged. This makes the risks similar to those in X-Ray therapy. Using gold nanoparticles to deliver platinum to cancer tumours may be a way to reduce the side effects of platinum cancer therapy. The key is that the toxicity level of platinum depends upon the molecules it is bonded to. So the researchers chose compounds of platinum containing molecule that has low toxicity to attach to the gold nanoparticles. If this treatment were to be developed, the platinum bearing nanoparticle could be escorted to the affected site where an injected acidic solution awaits, changing the platinum into its toxic state. Moreover, only the cancer cells will be killed in the process. This would be a far better approach to targeting cancer cells than available currently. Based on our research, we envisage that this practise will become common place within the next three to five years. [7]

Nanoparticles in Sensors

Sensors based upon nanoparticles or nanowires can detect proteins related to specific types of cancer cells in blood samples. This could allow early detection of cancer. T2 Biosystems uses super paramagnetic nanoparticles that bind to the cancer indicating protein and cluster together. These clusters provide a magnetic resonance signal indicating the presence of the cancer related protein. If this was introduced into future early cancer detection methods, the MRI scanner could be used to identify tumours at early stages, not just late stages. As the underpinning technologies for sensors are already in place, we estimate that nano-sensors will be in general use within the next five to eight years. [6]

The use of X-Ray Therapy

X-ray therapy is a way in which nanotechnology can be used to destroy cancerous tumours in the form of a nanoparticle called nbtxr3. The nbtxr3 nanoparticles, when stimulated by x-rays, produce electrons that lead to the destruction of cancer tumours to which they have attached themselves and so acts as a lower powered x-ray. This is intended to replace radiation therapy, as it has a considerably reduced risk of radiation sickness caused by damage to healthy tissue. This therapy is due to go on trial and we predict that it will be of practical use in the next five to ten years. [6]

Immune Response

A technique to increase the number of cancer fighting immune cells in cancer tumours would be a contrast to irradiating them. Nanoparticles containing drug molecules called interleukins are attached to certain immune cells (T-cells). The concept is that when the T-cells reach a tumour the nanoparticles release the drug molecules, which cause the T-cells to reproduce. If enough T-cells are reproduced in the cancer tumour the cancer can be destroyed. This method has previously been tested on laboratory mice with very good results; nevertheless further research needs to be done before doctors can trial this treatment on humans. Combining the effects of magnetic nanoparticles that attach to cancer cells in the blood stream may allow the cancer cells to be removed before they establish new tumours.

One of the characteristics of cancers is its ability to supress the immune system. This prevents the body’s own defence system from eradicating the disease. Using polymer nanoparticles it is possible to deliver a molecule called JSI-124 to cancer tumours. This molecule weakens the ability of the cancer cells to inhibit the immune system, possibly slowing the growth of cancer tumours. Consequently this would give doctors more to time to investigate the tumour and confirm the most effective treatments.

At this point in time we feel that this technology is in its infancy and will take in the region of ten years to reach a stage of maturity.

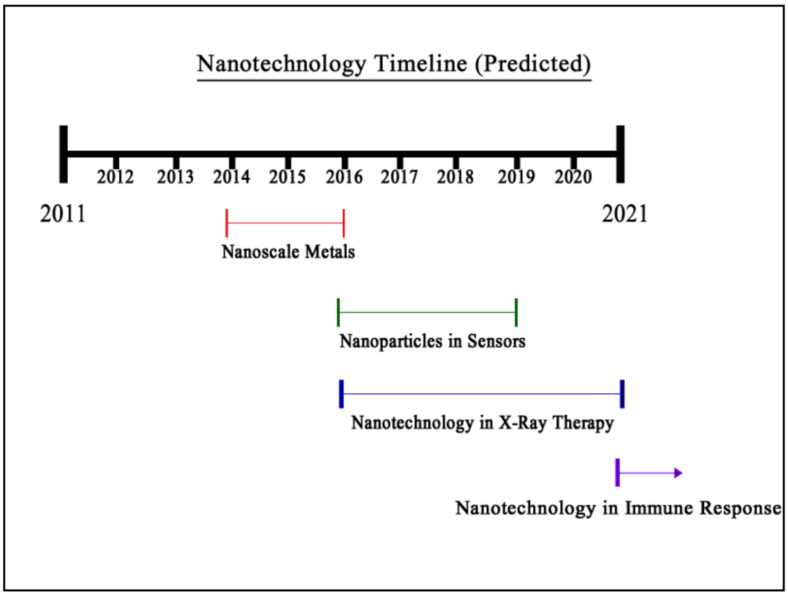


FIGURE 6

Ethics:

Ethics with respect to medicine are the principles and moral values of proper medical conduct. In many ways the ethical issues inherent in the use of nanotechnology are generic to biological medicine. These include concerns about the toxicity and environmental impact of nanomaterials and their potential effects on global economics, as well as speculation about various doomsday scenarios.
Imagine you have a terminal disease, and there's new research to indicate a possible treatment, but no clinical trials have been conducted in humans yet. Should you be allowed to try this new therapy? If you don't have long to live, should you be concerned about possible side effects? These are just some of the ethical aspects which prevent the uses of nanotechnology in modern day medicine. For example, earlier we discussed the success nanoparticles containing interleukins had on supporting a mouse's immune system against cancer. The drug showed a positive effect on the mouse's immune system without any side effects. However doctors cannot know with certainty that the drug will have the same result on humans. Lack of understanding or regulation of nano-materials could harm people as well as the environment
There is more than one method in which nanotechnology could be used to treat cancers:

1) To prevent someone from acquiring cancer
2) To stop cancer in its early stages
3) To stop cancer in its late stages

All three of these aspects have counter ethical issues which oppose the ideas of introducing new nano methods of treating cancer. If someone has a history of cancer in their family however has no indications of the type of cancer yet, can we justify treating them to prevent them acquiring that cancer? If we do, we are playing against nature, not with it. Religion has a big influence on what is right and wrong in society. By attempting to eliminate cancer from one's body, we are accused of "playing God".

Nanotechnology has the capability to create radical change, thus it is put into the category of "disruptive" technology. There are many ways in which nanotechnology can be used to change our lives, which raises some very controversial ethical questions. For one, if nanotechnology could be used to help us live longer, what would be the restrictions? If restrictions were out of the question then what problems could arise with making these benefits available to all? [8]

Moreover, if it was made possible for us to substantially halt the ageing process using Nano-medicine to repair damaged cells at a molecular level, our economy and society would dramatically change. People argue whether nanotechnology would be a plausible investment.

This leads us on to another major ethical issue which is that poorer countries such as India and Sub-Saharan Africa lack even the basic health care. Would it not be wrong to invest large amounts of money in cutting edge technologies as it could be a ridiculous waste of money?

Should we not be focusing on helping undeveloped countries by supplying even the simplest of things such as a clean water supplies and basic education? [9]

The Centre for Responsible Nanotechnology (CRN) is a non-profit organisation whose main concerns are the social and environmental implications of the advances in nanotechnology. CRN engages individuals and groups to better understand the implications of molecular manufacturing and to focus on the real risks and benefits of the technology. [10]

Disadvantages:

In spite of the possibilities and the advancements that nanotechnology offers to the world, there also remains debates on the practicality of investing in nanotechnology. People understand the advancements that have been made since the introduction of nanotechnology however they lack knowledge of the concealed dangers and possible risks involved with nanotechnology.

Some of the challenges of most drug delivery systems include poor solubility, intestinal absorption, therapeutic effectiveness, side effects, and plasma fluctuations of drugs which either fall below the smallest effective concentrations or exceed the harmless therapeutic concentrations. Researchers and scientists have not yet delved into what could be done to reduce these risks. [11]

Nanoparticles have large surfaces. This makes them vulnerable to absorption by macromolecules in the human body. They can hinder biological processes such as digestion, thus preventing the body from functioning normally.

On average, 1 in 3 people acquire a form of cancer. Although it may seem impossible, if nobody ever died from cancer, we would have to go a step further than China and enforce a law that prevents people from having children, thus avoiding overpopulation. Hundreds of hospitals would need to be created to adhere to the demands of those who are being treated. This could only be achieved through huge investments by the government. [12]

Thought experiment

With the above in mind, it is our proposition that we could develop a nanodevice capable of searching, recognising, eradicating cancer cells and finally making decisions using silicon technology. For the purpose of this research paper, we will refer to this device as a Nano-Homing Device (NHD). This device would have the capacity to make decisions through the integration of an on board nanocomputer (manufactured from silicon), a supply of an appropriate drug and several binding sites to determine the concentration of specific molecules. The drug would be released when a cell is recognised as cancerous.

The nanodevice will circulate through the body system and would intermittently sample its surroundings by determining whether the binding sites were or were not engaged. Occupancy results will allow determination of concentration. Monoclonal antibodies are able to bind to only a single type of protein or other antigen, and have not proven well against the majority of cancers. The cancer killing NHD we propose could include several different binding sites and so could therefore monitor the concentrations of several diverse types of molecules. The device could determine whether the profiling of concentrations fit a pre-programmed template cancerous profile and so would therefore release the “poison” when a cancerous profile is encountered.

The NHD could therefore determine that it was located in the lungs for example. If the aim was to kill a cancer, the device in the lungs would release its poison. Total control over locality of the device’s activities could therefore be accomplished.

The silicon nanodevice could be re-programmed to attack a diverse variety of targets. This general design could provide a flexible method of terminating unwelcome structures (invasive bacterial infestations, etc.)

Conclusion:

This paper has argued that nanotechnology will make a significant contribution to discovering the cure for cancer. It has also argued that a hybrid approach which is based on a combination of nanodevices could form the basis for a new approach to the cure for cancer.

There are a number of reasons as to why we feel that the use of nanotechnology in its various forms will provide a cure for cancer; some of which we have outlined in this research paper and have summarised below:

Nanotechnology is unique in that it allows many fields to contribute to the cure for cancer. This multi-dimensional and multi-disciplined approach which is not reliant on a single area or technology is more likely to achieve results in the cure for cancer.

The value of nanoparticles lies in the fact that the chemicals chosen for the basis of the nanodevices can be made of non-toxic materials such as carbon which means that the body's immune system doesn't attack them. They can bind tightly to a variety of molecules and deliver these directly into a tumour. Due to these nanoparticles only being two to eight nanometres in diameter, they are easy for major organs such as the kidneys to clear from the body before they block up blood vessels, a long-standing problem in nanoparticle therapy.

Moreover, one of the unique features of nanoparticles is that materials reduced to the nanoscale can show different properties compared to what they exhibit on a macroscale. This can be used to address a major challenge in chemotherapy which is that tumour cells develop mechanisms to pump drugs back out. However, when the drug is bound to a nanoparticle, the combination is too large for the pump, so tumours would in effect have a hard time evolving resistance.

The combination of silicon and nanotechnology will be a potent combination which can be used to conquer cancer. The use of decision making hardware in combination with the use of non-toxic materials to deliver targeted drugs has the capability to address the current issue of the toxicity of drugs and the targeted and focussed approach as opposed to a body wide approach to cancer. Moore's law provides us with a basis for predicting the roadmap for the integration of computer and nanotechnology. Using Moore's law we have predicted that nanotechnology in the treatment of cancer would be a wise investment as it would make an effective contribution to the abolition of cancer from our society.

References

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Image References

Picture on first page: http://www.voyle.net/Extra%202005%20Images/21-01-2005-2.jpg

Figure 1(Created using pictures): http://www.vtaide.com/png/images/atom.jpg
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Figure 2: http://mayoresearch.mayo.edu/mayo/research/dev_lab/images/single_drug.gif

Figure 3: Created using this diagram http://www.understandingnano.com/nanoshells.jpg

Figure 4:http://www.gibthai.com/gibthaiv2/userfiles/image/New%20Products/Qdot/Qot-1.jpg

Figure 5: http://spie.org/x42061.xml?ArticleID=x42061

Figure 6: Created ourselves