

The use of Nanotechnology in the Improvement of Diagnostic and Treatment Techniques for Cancer

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Abstract

Without realising it, the phenomenon of nanotechnology has been around us for centuries. Medieval artists used golden nanoparticles to achieve a shimmering shade of red on church windows. It is only in recent years however, that science has begun to explore the fascinating potential that exists in the engineering of particles at the nanoscale. From a medical perspective, the ability to combat disease and ill health must begin from the molecular or cellular level. It is therefore not surprising that the effect the efficient manipulation of such technology could have on the field of medicine in particular, has been recognised by many. In this research paper we shall aim to focus on the changes this may bring to the diagnostic and therapeutic process of a disease that contributes to 13% of all deaths worldwide, cancer.

Introduction

What is nanotechnology?

By definition nanotechnology is the controlling of matter at a scale of approximately 1- 100 nanometres. But dealing with such miniature dimensions means materials behave uniquely. In fact their physical, chemical, and biological properties differ fundamentally from those of

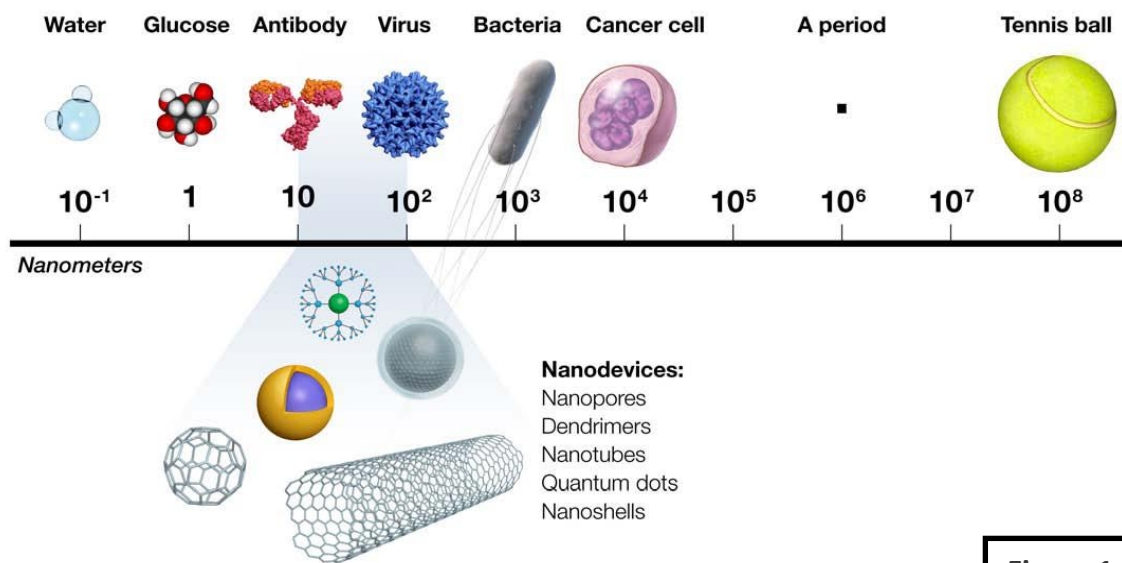


Figure 1

the corresponding bulk material. Figure 1 above shows that a nanodevice can be up to 100 times smaller than a single prokaryotic cell. Furthermore, by dealing with materials at the nanoscale, scientists have found themselves able to control the principle characteristics of a material, such as melting point, magnetism and colour, without altering the chemical composition of that material. Many may wonder why such remarkable changes in properties have never been observed when going for the macro to micro scale. This is because working at the nanoscale dramatically increases the relative surface area of a material and this is thought to be the main contributor to the extraordinary change in properties seen. It is believed that utilising these properties in medicine, could lead to great developments in

creating drug delivery systems, efficient diagnostic techniques as well as many other applications.

The reason that progress in developing the technology has been so recent is primarily due to the fact nanotechnology is very much reliant on technological advances. The invention of the Atomic Microscope in 1986 gave scientists increasing control to attempt to manipulate the atomic composition of materials.

Current uses and research

It was in 1959, when Richard Feynman, delivered his speech “There’s Plenty of Room at the Bottom” that scientists realised the capacity for nanotechnology in modern day. His ideas would bring about the concept of building from molecules rather than attempting to ‘shrink’ things down. Already, several applications centred on this principle have been introduced into modern life and are either in use or being researched.

For example, the free radicals generated during an allergic reaction may be trapped using buckyballs. Subsequently, the inflammation will be blocked and the effects of the infection will be limited.

Another example is using nanocapsules containing antibiotics to coat burn dressings. If an infection results from the burn wound, the nanocapsules will break open and release the antibiotics to combat the infection. The infection will be treated much faster and also the dressing does not have to be changed as often.

Medicine...current & future prospects

Many would argue that by modern standards, medical methods could be improved hugely. When compared to the computing industry for example, some people feel it is fair to say we can do much better. Let us put this accusation into perspective. When a person experiences pain in the shoulder, they would need to see a doctor, who would prescribe them a drug, which would in turn have to be induced into the body by the various means possible. Now this drug is not only delivered to the affected area but is also received by the healthy parts of the body. As a consequence of this, the required volume of the drug must be given in carefully calculated doses otherwise the healthier parts of the body could be essentially poisoned by the drug. Nanoengineered drugs can be designed for specific individuals and their illness. This means less trial and error and waste of prescribed medicine by the physician, fewer side effects and faster physiological responses. This can be applied to all illnesses, from a cold to cancer.

With that in mind it is no surprise medicine is a field that has been particularly excited by recent developments in nanotechnology. All aspects of medicine, including drug delivery, therapeutics and diagnostics rely on professionals looking closely at the biological molecules involved. The very first signs of a disease or illness occur at the cellular level. The current equipment available suffers from the great disadvantage of only being able to look at any abnormality at the macroscopic level. Once the treatment has been administered, we are fortunate in the sense that the regenerative ability of our cells can take over. If physicians are given the chance to work at the molecular level, they can fight the disease at its roots thereby perhaps eliminating the need for the natural regenerative process to occur, making faster and more efficient treatment possible. Today, progress has been made in developing tools that can help meet these requirements:

As will be demonstrated in the discussion, the impact this technology could have on medicine in the future will mean that scientific research in the field of nanotechnology is likely to greatly accelerate. In 2003, American Congress passed a bill authorizing \$3.7 billion to fund nanotechnology research, including medical applications. With the financial backing of governments, the applications mentioned above could very soon become the norm in medical practice.

Discussion

Genetics & statistics of Cancer

Before we delve fully into the main issue of this project which deals with applications of nanotechnology in cancer prevention, detection and treatment, we must address the underlying causes and the genetic mechanisms involved in cancer.

Cancer is a genetically rooted disease involving cells that divide and/or grow abnormally. It involves the simultaneous occurrence of two general categories of cellular malfunctions:

The first category causes the replication of a cell to become permanently enabled due to a natural or carcinogen-induced genetic mutation, chromosome translocation or gene amplification (genetic instability).

The second category is also due to genetic mutations, and causes the apoptosis complex, also known as the suicide complex, to become permanently disabled (Figure 2). As stated, both of these problems must occur in the same cell, at the same time, in order to cause cancer.

In this illustration, we can see how even a single nucleotide base inserted (or removed) out of sequence can cause the entire subsequent chain of amino acids, which are the building blocks of proteins, to be incorrect. When this happens in the gene sequence that codes for the protein(s) responsible for apoptosis or damping cell division, the cell permanently loses the ability to carry out that particular function (image source: <http://ghr.nlm.nih.gov/ghr/>). It must be added that many other mutations can be also cancerous

Insertion mutation

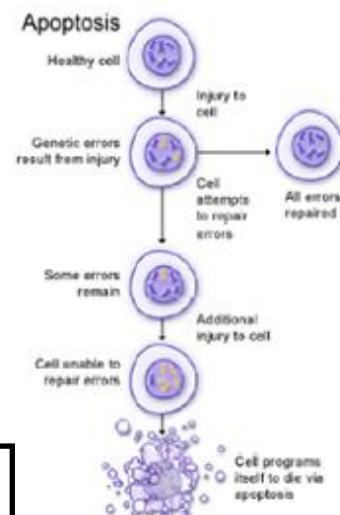
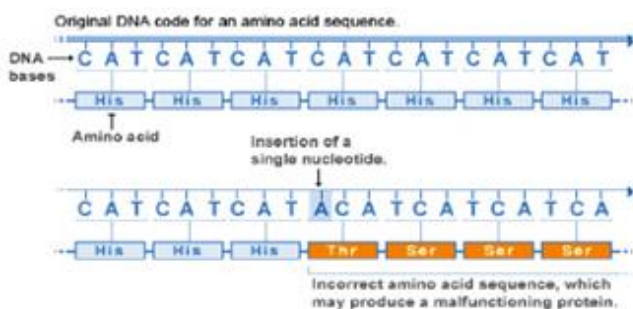


Figure 2

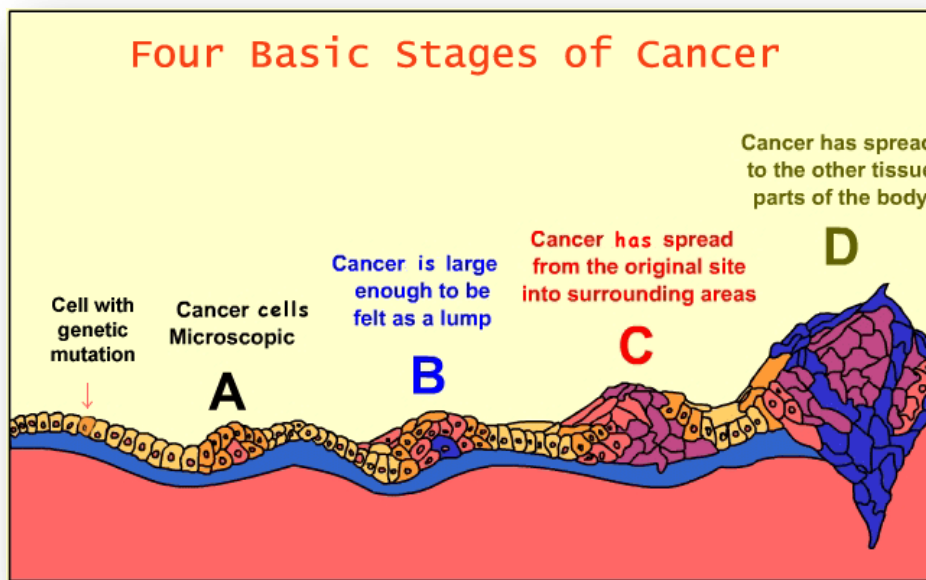


Figure 4

Eventually, when the tumour grows large enough, some of the tumour cells can find their way into the bloodstream, forming tumours in other parts of the body. This latter phenomenon is known as metastasis. It effectively multiplies the cancer as well as its effects, and eventually will prove fatal to the patient. This progression is shown in Figure 4 above.

	England	Wales	Scotland	N.Ireland	UK
Cases					
Males	123,131	9,151	13,147	3,927	149,356
Females	122,196	8,312	14,329	3,798	148,635
Persons	245,327	17,463	27,476	7,725	297,991
Crude rate per 100,000 population					
Males	490.3	629.4	528.9	455.6	499.2
Females	470.4	544.7	539.0	423.3	478.6
Persons	480.2	586.0	534.1	439.1	488.7

Figure 3 - number of new cases and rates of all cancers excluding non-melanoma skin cancer, UK, 2007

As figure 3 above shows, cancer is a leading cause of death in the UK. By 2020, it is estimated that, there will be 15 million new cases annually. In 1950, the death rate per 100,000 for cancer was 193.9, and in 2003 it was 193.1. Compared with heart disease which also has large mortality rates, it had a death rate per 100,000 of 568.8 in 1950; it only had a death rate of 231.5 in 2003. This shows current diagnosing and treating techniques do not suffice and still have a long way to go.

Current diagnosis of cancer

At present, diagnostic tests can occur only once a patient displays various symptoms such as a change in bowel/bladder habits, unusual bleeding or a lump in the breast/testes. To confirm the symptoms are a consequence of cancerous growth, an image of the suspected area using a Computed Tomography scan for example and interpreting it. Imaging may indicate abnormal growth but a biopsy is necessary to confirm it is cancer. This involves extracting a sample from the abnormal cells from which a pathologist will deduce whether the tumour is cancerous, the type of cancer present and the speed at which cells are capable of dividing. The final process is to stage the cancer to see the extent at which it has spread; this can often be achieved by seeing if there are cancerous cells present in the lymph nodes. All of the above procedures are required to ensure the most effective treatment can be given.

Limitations of these methods

Current imaging techniques lie at the tissue level and so fail to detect all cancer cells. The image quality and experience factors have to be taken in to account as they can result in a procedure being misinterpreted which produces false positives and false negatives. Additional time and tests for confirmation is needed which reduces efficiency and survival chances as the cancer will be metastasising.

Current Treatments of Cancer

Amongst several treatment options an oncologist can inform you of, four are most common in current practice – surgery, chemotherapy, radiation therapy and biologic therapy. If these measures fail, then the patient has a less than 10% chance of successful treatment from other sources.

Surgical procedures are used to remove entire tumours or as much of the cancerous tissue as possible.

Chemotherapy is an antineoplastic which has one of the highest success rates but differs from surgery as it affects the entire body.

The other form of treatment uses radiation to prevent cancer cells from dividing by damaging their DNA. This prevents mitosis from occurring and the high sensitivity of the cancer to the radiation means they generally die when treated. Healthy cells maybe damaged but are often able to fully recover.

Limitations of these methods

- Chemotherapy aims to target rapidly dividing cells and therefore affects cells such as those found on the lining of the stomach and follicle cells as well as cancer cells. This damage to the hair follicle cells causes rapid hair loss and with it, social difficulties for the recipient may arise.
- The desired effects are limited and the patient has to endure severe side effects. These include nausea, neuropathy, hair loss, fatigue, and compromised immune function.
- In surgery, there is a risk of damaging the tumour which in turn can penetrate cancer cells in to the blood vessels leading to further metastasis
- Chemotherapeutic drugs are highly toxic and therefore are carcinogens themselves.

Uses of Nanotechnology in Cancer

There are two main issues which need to be considered when using nanotechnology in a biological system:

- To be large enough to ensure they don't just pass through the body.
- To be small enough to ensure they don't accumulate in vital organs and create toxicity problems.

As has been seen, the imaging techniques used to diagnose cancer simply do not have the capacity to detect the early molecular changes that occur in the disease. Here, the sensitivity of nanotechnology is crucial. This next part of the discussion will aim to analyse the success and viability of contemporary research.

Assessing the use of nanotechnology to diagnose cancer

Imaging

Current imaging methods can only readily detect cancers once they have made a visible change to a tissue, after which thousands of cells will have proliferated and perhaps metastasised.

If cancerous cells could somehow be tagged for detection by conventional scanning devices, the detection of cancer would be easier. For that something that specifically identifies a cancerous cell and enables it to be seen is necessary. This can be achieved through nanotechnology.

Quantum Dots

Quantum dots are semiconductor structures with physical dimensions less than the Bohr radius (distance between a hydrogen nucleus and its orbiting electron), typically between 2-10nm. They have the novel property of having an extremely narrow emission spectrum. This gives them the unique ability to emit light representing every colour in the visible spectrum from the same elemental material. Developments are underway to create the world's first solid state lighting sources. The colour of the molecular light sources depends solely on particle size. Quantum dots emit light upon binding to functional groups of molecules and hence could prove to be crucial tools in the diagnosis of disease.

Molecular labelling has become a common diagnostic tool in cancer. The light emitting properties of a group of restricted radioactive elements, chemical dyes and protein molecules are being used currently as a method to label and visualise DNA and protein molecules. The limitations of this current method are that radioactive markers have short lifespans; organic dyes come in a limited number of glows and can lose their colour quickly. The multiple-molecule types present in a cell means there is need of a more reliable and accurate system for labelling flourophores. Flourophores are the functional groups of a molecule and will absorb energy of a specific wavelength, re-emit the energy and become fluorescent. The light emitted is captured by a computer, displayed on a video screen as images so physicians are able to give an accurate diagnoses.

Quantum dots they do not encounter the limitations that chemical and organic dyes do. Quantum dots are extremely stable; the particle size and composition can be changed which can alter the emission wavelength continuously. Also, a single light source can be used for the activation of all coloured dots simultaneously. For instance, Gao et al. successfully injected three different quantum dots in different areas of a mouse using a single light source, as shown in figure 5.

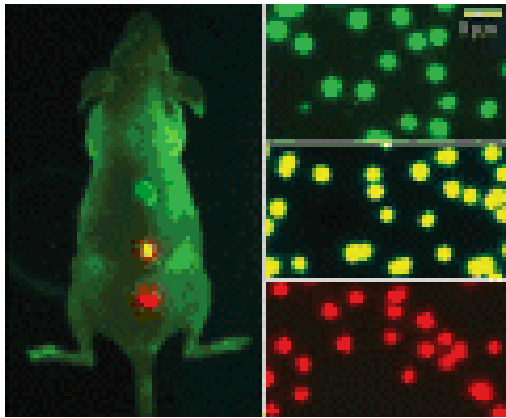
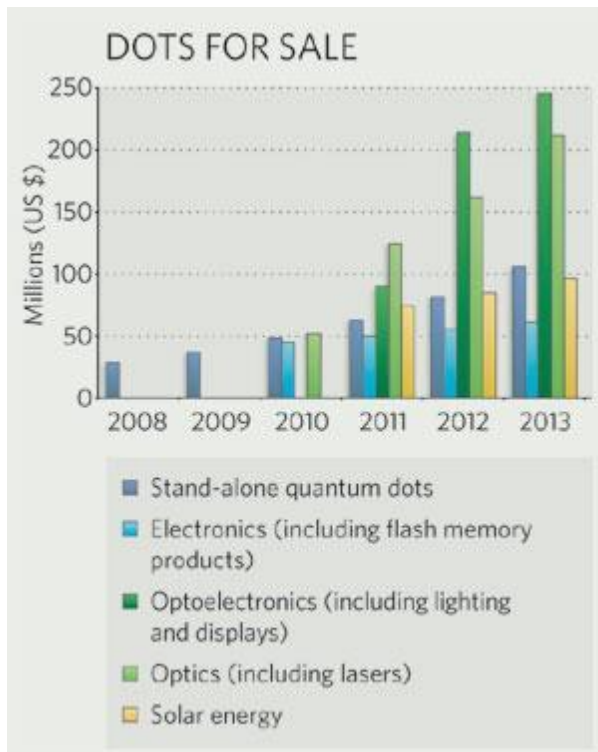


Figure 5

This method overcomes all the weaknesses of current molecular labelling methods. False positives and false negatives will be less likely to occur; so this is a financially viable option in the context that recurring unnecessary tests are not needed. Time will be saved for the physicians and patients; cancer will be detected in its early stages so chances of survival will be much better.

Although money is saved from not repeating tests, a key barrier for the use of quantum dots is price: quantum dots cost from US\$3,000 to \$10,000 per gram which restricts their applications to specialised procedures. Conversely, industry analysts are predicting rapid growth for the market; it is estimated that products relying on quantum dots would increase from \$28.6 million to \$721 million by 2013. Figure 6 below demonstrates this.



Higher demands mean costs will tumble and use of quantum dots in diagnosing cancer has the potential to become much cheaper and more common.

Figure 6

Evidently, the hopeful use of quantum dots in humans may be not be appropriate. This is due to the quantum dot's composition of heavy metals and reports of cytotoxicity from Derfus et al. Also, non-polymer-protected quantum dots, when exposed to ultraviolet light, are unstable and there is evidence by Derfus et al. to show that they release toxic cadmium.

Having evaluated this method, we believe it is appropriate due to survival rates being poor and the inability of detecting cancers early. Goa X's et al. research suggests that modifying the quantum dot can minimise the release of toxic metals when exposed to UV light. With further research, this method's few other limitations can also be overcome and it can be used as an effective and efficient diagnostic tool, that can have huge impacts on the improvement of imaging techniques for cancer.

Assessing the use of nanotechnology to treat cancer

Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three methods risk damage to normal tissues or incomplete eradication of the cancer. Nanotechnology offers the means to aim therapies directly and selectively at cancerous cells.

Nanocarriers

Conventional chemotherapy employs drugs that are known to kill cancer cells effectively. But these cytotoxic drugs kill healthy cells in addition to tumour cells, leading to adverse side effects. Nanoparticles can be used as drug carriers for chemotherapeutics to deliver medication directly to the tumour while sparing healthy tissue. Nanocarriers have several advantages over conventional chemotherapy. They can:
Protect drugs from being degraded in the body before they reach their target.

- Enhance the absorption of drugs into tumours and into the cancerous cells themselves.
- Allow for better control over the timing and distribution of drugs to the tissue, making it easier for oncologists to assess how well they work.
- Prevent drugs from interacting with normal cells, thus avoiding side effects.

Biologists and nanotechnologists can use nanobiotechnology to create a solution which may include the use of sustained, controlled and more accurately targeted use of chemotherapy.

Nanobiotechnology will change the way drugs such as Taxol, the normal drug for cancer patients, are produced. Paclitaxel, a standard form of Taxol is an anti-cancer chemotherapy drug (antineoplastic). Using nanotechnology, it inhibits proliferation and has the property of encouraging apoptosis. It binds to and blocks the function of the apoptosis inhibitor protein (B-cell Leukemia 2). It is one of the most commercially successful cancer drugs due to its impressive therapeutic abilities. Results show paclitaxel which is formulated by Vitamin E TPGS-emulsified PLGA nanoparticles can be at least 18 times more effective than standard paclitaxel after 24 hours of cell culture. These are potentially huge improvements from the way chemotherapy is being used currently therefore this is an appropriate method.

However, like with any drug there are side effects that are similar when using standard Taxol, but they are limited as the damage to healthy cells is limited. Having evaluated this method, we think it is viable and appropriate.

Nanoshells - Destruction from within

Moving away from conventional chemotherapeutic agents that activate normal molecular mechanisms to induce cell death, researchers are exploring ways to physically destroy cancerous cells from within. One such technology, nanoshells, is being used in the laboratory to thermally destroy tumours from the inside. Nanoshells can be designed to absorb light of different frequencies, generating heat (hyperthermia). Once the cancer cells take up the nanoshells (via active targeting), scientists apply near-infrared light that is absorbed by the nanoshells, creating an intense heat inside the tumour that selectively kills tumour cells without disturbing neighbouring healthy cells and in doing so invasive surgical procedures are avoided. Similarly, new targeted magnetic nanoparticles are in development that will both be visible through Magnetic Resonance Imaging (MRI) and can also destroy cells by hyperthermia.

Example of an application – Nanotechnology in skin cancer

To demonstrate the viability of the nanotechnology-based treatments, let us consider melanoma. Melanoma, a form of skin cancer, is caused primarily by ultraviolet radiation from the Sun. The current method of preventive treatment against bombardment with this kind of harmful radiation involves suspending a substance that either absorbs or scatters ultraviolet radiation in a thick emulsion.

We use this emulsion, called sunscreen, to coat our skin prior to prolonged exposure to sunlight. Some of the problems with this method are that this emulsion can be easily

rubbed off and can lose its effectiveness over time, thus needing to be reapplied periodically.

An even bigger problem is that we leave openings in the sunscreen coating during sunscreen application due to macro-scale and micro-scale imperfections in our skin. This allows the Ultra Violet (UV) radiation to permeate through the dead layer of skin, spreading out to a wider area due to slit diffraction and causing more widespread damage.

Some recent works have shown that it is possible to tag specific types of cells with nanoparticles by joining them to targeting agents designed to recognise cell-specific surface proteins. Nanoparticles attached to desired drugs or substances can be joined to short peptide chains, proteins or artificial nanobodies.

If we manufacture nanoparticles attached to UV scattering substances like zinc oxide (ZnO) and titanium oxide (TiO₂) and specifically target these nanoparticles to skin cell surface proteins, we can effectively coat these cells with sunscreen on the nanoscale.

With this nanotechnology-based preventive treatment method, we would effectively eliminate most of the problems mentioned above. If the cells can be coated directly, the problem of diffraction in case where an area is sparsely coated will be eliminated.

The most important issue to consider in this form of treatment is, of course, the toxicity of the substance that is used. The biochemical effects of a substance on the patient's health must be thoroughly evaluated by standard laboratory testing procedures as well as clinical trials before this treatment can be safely implemented. However, we believe such tests could be successfully performed within a practical timeframe based on the current technological resources available.

Implications of Nanotechnology

The ramifications must be considered for the long term because nanoparticles in the lungs of some mice have been the cause of their death and the presence of some nanostructures in water has caused brain damage in fish. If nanoparticles are taken up by cells, they can enter our food chain through bacteria and pose major health risks. These are preliminary results but they hint we have to be cautious in the application of nanotechnology.

Robert Freitas, a researcher, holds a vision of nanomedicine. He believes that the creation of nanorobots as shown in figure 7, will allow us to inspect, repair, digest unwanted pathogens in our body and

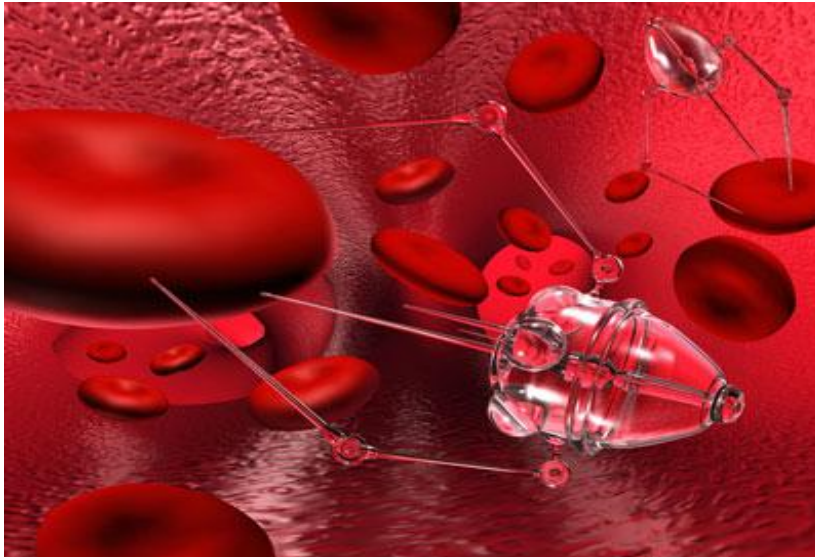


Figure 7.

A Nano robot?

defective chromosomes can be replaced. If these methods are successful, then ageing and death can be prevented indefinitely.

Perhaps, this vision of reconstructing ourselves is wrong. The theologian Ted Peters, raises the question of if we are 'playing God' by enhancing ourselves using nanotechnology. This approach will not be accepted from a religious perspective and may lead to social implications, such as huge clashes between Islamic, Christian values and scientific values. Humans have evolved and achieved much; maybe this is a step too far and therefore a major ethical concern.

Elaborating on Freitas's point, the advances in health care could have an impact on the concept of being 'sick' or 'well'. For example, it will have to be decided whether ageing is an 'illness' such as cancer. This could lead to situations such as some individuals being allowed to slow their ageing process whilst others are dying from cancer.

Following on from Ted Peter's point, it has three understandings: learn God's secrets, obtain power over life and death, and influence human evolution. Naturally, we have white blood cells to fight pathogens and they perform their function adequately, so why do we need molecular machines inside us to fight infections? It seems very unnatural. Everything up to the 21st century has naturally occurred. If we meddle in things that we can't fully comprehend, then perhaps there will be devastating unforeseen consequences to human health and our environment.

Conclusion

As has been demonstrated above, nanotechnology has rapidly transformed itself from the vague fantasy of Richard Feynman, into an industry that is radically influencing our health care system. It has been seen how nanodevices outperform modern instrumental techniques in several aspects of diagnosis and treatment for cancer.

With regards to cancer, or perhaps even in medicine as a whole, it is clear that these devices will continue to have a degree of influence in numerous areas such as drug delivery systems

and imaging techniques. But the underlying issue we have aimed to address in this paper is whether or not this technology has the capacity to become the main authority in medical practice. The benefits are countless but one must remember that, as we attempt to recover from a widespread recession, the mass implementation of nanomedicine is unlikely to be an economic priority. Moreover, the patient demand must be significant if health institutions are to use the technology. In our opinion, the possible apprehension of prominent academics may be a significant setback in achieving this. Having said that, we are hopeful that the future for nanotechnology in medicine is bright and we feel there is no doubt that the coming years will see increasing use of nanotechnology in the fight against cancer.

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