

Nanotechnology:
A New Revolution in Primary Care & Diagnostics

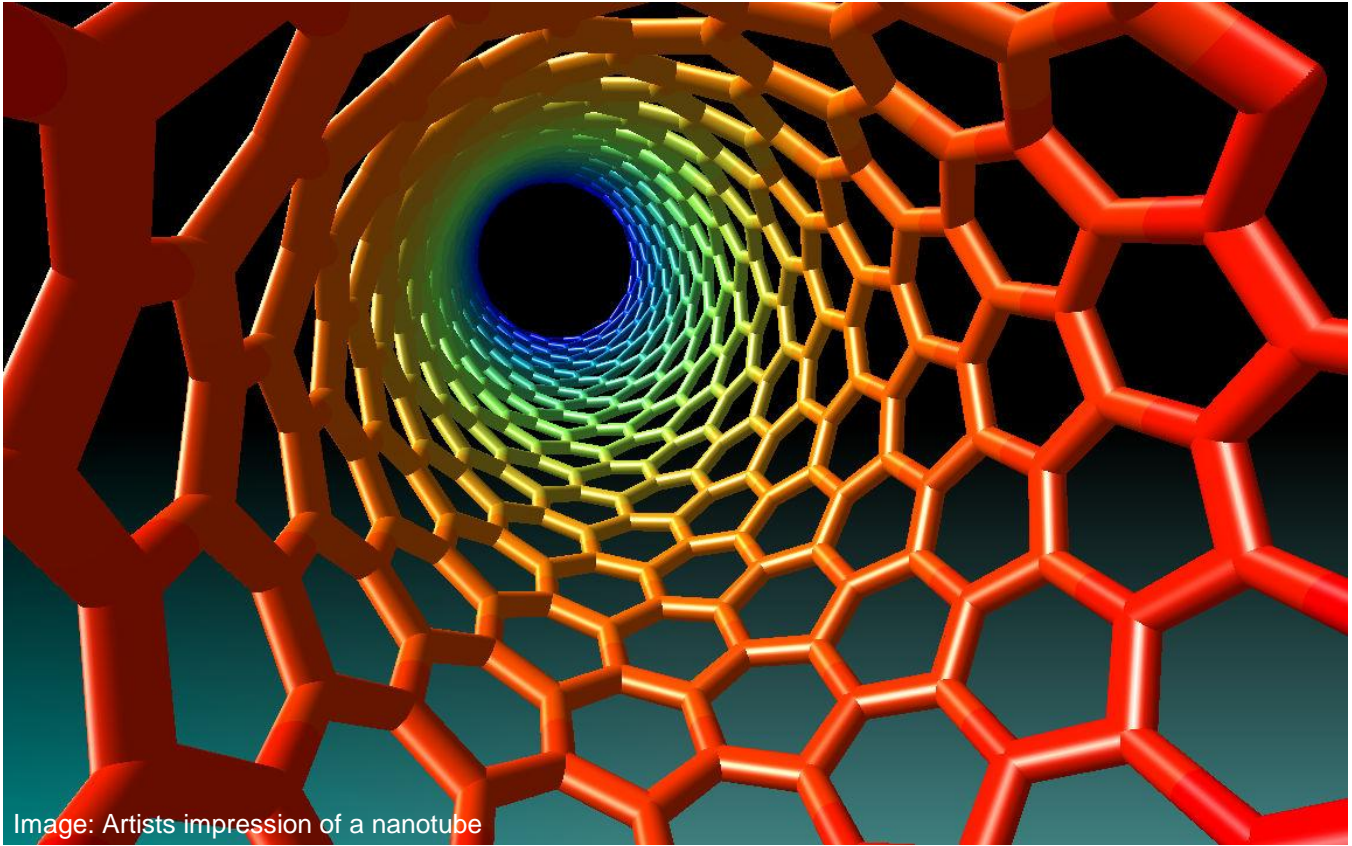


Image: Artists impression of a nanotube

By Jonathan Harvey

PASS WITH MERIT

(130 words over limit)

Research Paper Based on Pathology Lectures at Medlink 2010

Abstract

This paper takes a unique approach by looking at the possible applications of nanotechnology and nanoscale devices in a primary care environment by analysing both current and past research, and investigating how it can be advanced and refined in order to equip general practitioners with the tools they need to rapidly and accurately diagnose cancer. Since arriving at this discovery, I have decided to also explore other avenues of research, such as personalised health monitoring and diagnostics.

Introduction

All of biology is a form of nanotechnology which began 3.5 billion years ago; nature has created nanostructures for billions of years. Each living creature is made up of tiny cells, which are themselves constructed of nano scale building blocks; bio-machines such as proteins, lipids, nucleic acids and other complex biological molecules which perform such tasks as manipulating genetic material and supplying energy. Taniguchi (1974) stated that, “*Nanotechnology mainly consists of the processing of, separation, consolidation and deformation of materials by one atom or by one molecule*”. Basically nanotechnology is simply building from atoms, trying to copy nature; nanometre scale objects made of inorganic materials are used in biomedical research, disease diagnosis and therapy. The most important requirement defining nanotechnology is that the nanostructure has special properties that are exclusively due to its nanoscale proportions.

Fundamental concepts of nanotechnology

One nanometre is one billionth or 10^{-9} of a metre. By comparison:

- A molecule is 1nm
- DNA is 10nm
- A virus is 100nm
- Bacteria is 1000nm
- A pollen grain is 100,000nm

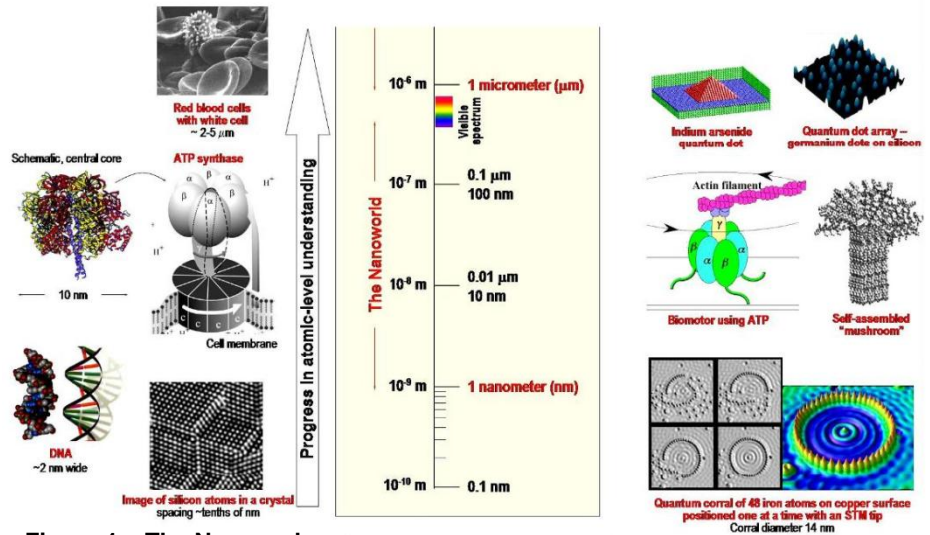


Figure 1 – The Nanoscale

To put this scale into a different context, the comparative size of a micrometre to a metre is the same as that of a marble to the size of the Earth.

Two main approaches are used in nanotechnology. In the ‘top down’ approach nano objects are constructed from larger entities without atomic level.

In the 'bottoms up' approach (Drexler 1986), materials and devices are built from molecular components that assemble themselves chemically by principles of molecular recognition.

The History of Nanotechnology and its Medical Applications

Over 100 years ago, Albert Einstein (1905) calculated the size of a single sugar molecule, from his experimental data on the diffusion of sugar in water. His work showed that each molecule measures about a nanometre in diameter. This initial scientific breakthrough showed that at a billionth of a metre, the nanometre is the essence of small, and formed the birth of nanotechnology.

It was over 50 years later (1959) that Richard Feynman's famed talk '***There's plenty of room at the bottom***' discussed the real prospects of miniaturisation and acted as a catalyst for future research, '***We can make things that are very small that do what we want.***' He discussed cell movement, how cells manufacture various substances and hold information. In addition his research at that time also included the miniaturisation of computer components.

In order that scientists could make more rapid progress in the field of nanotechnology, he challenged physicists to make the electron microscope more powerful and Binnig (1981) created the scanning tunnelling microscope (STM). This is the point when nanotechnology and nanoscience got started. For the first time individual atoms could be imaged, to investigate structure surface atom by atom which was useful in the study of DNA molecules, cell division and the foundation of genetic properties. Experimental nanotechnology didn't come into its own until then, enabling scientists to identify genes that are responsible for a vast range of particular diseases including cancer research, diabetes, heart disease and childhood diseases. This discovery led to the discovery of fullerenes.

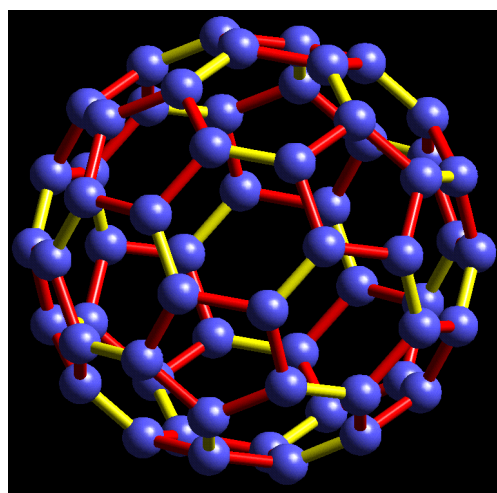


Figure 2 – Buckminsterfullerene

As demonstrated by the work of Smalley (1985) the 'buckminsterfullerene' (known as bucky balls) have the potential to form the basis of a more effective and controllable drug delivery system. Infected regions of the body are known to have different pH levels, and researchers hope to functionalise a buckyball by bonding it to molecules that react to change in pH, so that the drug is only released in the infected area. C_{60} are made of 60 carbon atoms arranged in a spherical shape. Because they are hollow, drugs could be enclosed within them so that they could be safely transported to where they are needed in the body. For example, insulin isn't given orally as it is broken down in the stomach and therefore has to be injected. Buckyballs (which measure 1 nanometre in diameter, the same as a sugar molecule, could be used to theoretically deliver insulin to the right place.

Eric Drexler (1986) published *'Engines of Creation: The Coming Era of Technology'*, considered to be the first book on the subject of nanotechnology, popularising the potential of molecular energy, describing what was later to be known as molecular nanotechnology (MNT). He proposed the futuristic idea of a Nano scale 'assembler' which would be able to build a copy of its self. He also described what might happen if a hypothetical self-replicating MNT went out of control.

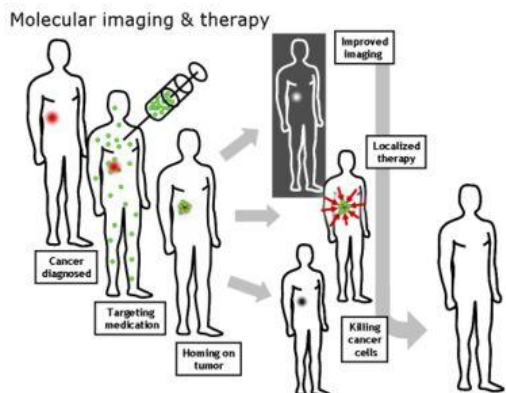


Figure 3 – Quantum dots used to locate and kill cancer cells

In another development, the synthesis and properties of semi-conductor nanocrystals was studied; this led to a fast and increasing number of metal and metal oxide nanoparticles and quantum dots, which in the future could be applied to treat cancer. The advantage that this treatment, like other nanotechnology research is that it aims therapies directly and selectively at cancerous cells.

The Atomic Force Microscope (AFM) pioneered by Binnig (1986) became the successor to the STM. It has the advantage over the STM in that it can provide very high resolution type scanning; microscopes with demonstrated resolution on the order of fractions of a nanometre. As one of the primary tools for imaging, measuring and manipulating matter at nanoscale it has been particularly important in the study of cancer, HIV, genetics and stem cell research. Defects in secretion and membrane fusion give rise to Diabetes, Alzheimer's disease, Parkinson's disease and Polycystic Ovarian Disease and Gitelman Disease associated with growth hormone deficiency.

Nanoparticles

The discovery and manufacture of nanotubes resulted directly from the research of bucky balls.

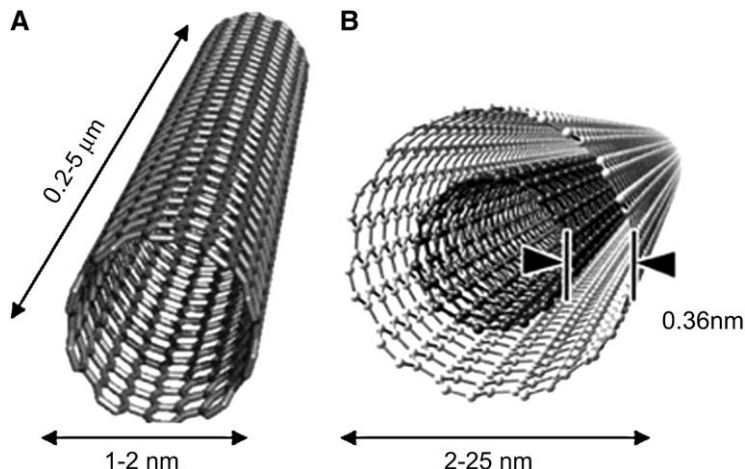


Figure 4: Dimensions of a Carbon Nanotube

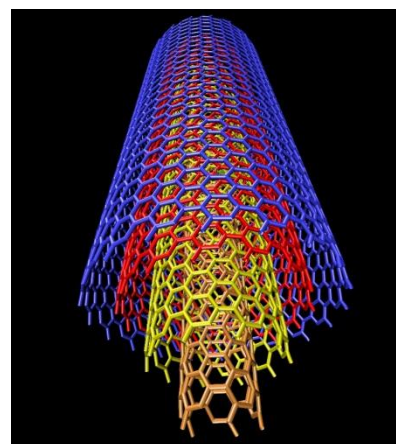


Figure 5: Multi-walled Carbon Nanotube

Fullerenes, discovered unexpectedly during laser spectroscopy experiments at Rice University by Iijima (1991) are forms of carbon that consist of spherical, cylindrical or ellipsoid arrangements of carbon atoms. Carbon nanotubes are 100x lighter and hundreds of times stronger than titanium, making its qualities potentially valuable. Research is underway using nanotubes in the construction of body armour, combat jackets that stop bullets and even monitor the condition of the wearer. In the future, sensors either worn or implanted could have the potential to monitor the condition of the soldier in response to fatigue or wounds and this information could be relayed directly back to medical staff.

Due to the high contraction/extension ratio, given an electric current, CNT's are thought to be potentially ideal to produce synthetic tissue to replace damaged muscle tissue. Cantilevers are made from CNT, are electronically conductive which allows for their use in STM and EFM (electronic force microscope). They can be modified at their ends with specific chemical and biological groups for high resolution functioning imaging to distinguish molecular states and composition in living tissues and cells. The introduction of a virtual reality system by Robinett (1993) being connected to a scanning, tunnelling microscope enabled the user for the first time to see, and touch the atoms. The ability to create a transistor from a nanotube has led to faster computers with the ability to offer speedier medical diagnosis. Improvements in material science have advanced the capabilities of MRI scanning.

From the information gathered I can conclude that nanotechnology research is proceeding on two main fronts, lab based diagnosis and in vivo diagnostics and therapeutics. In my discussion I will investigate how nanotechnology will provide GP's with the technology to rapidly and accurately diagnose cancer, and take a look at how nanotechnology can be used as a general diagnostic tool for health.

Discussion

All cancers begin in cells, the body's basic unit of life. Normally these cells grow and divide in controlled way to produce more cells needed to keep the body healthy; old and damaged cells die and are replaced with new cells. When the process goes wrong, the genetic material, (DNA) of a cell becomes damaged or changed, producing mutations that affect normal cell growth and division. Consequently, cells do not die when they should and new cells form where the body does not need them; these extra cells may form a tumour. Tumours can be benign or malignant; it is the malignant tumours that are cancerous and cells in these tumours can invade nearby tissue and spread to other parts of the body (*metastasis*).

About 7.6 million people die from cancer worldwide each year. In the UK the most common cancers are breast, lung, colorectal and prostate that accounted for more than half (53%) of the new cases of malignant cancer (excluding non-melanoma cancer) registered in 2008.

Whilst it is not possible to accurately define how many cancers are misdiagnosed by GP's the tabloids indicate at 1 in 4 (Daily Mail, March 2011).

Currently GP's often have difficulty in differentiating between the symptoms that indicate cancer or the symptoms that indicate a less serious illness, especially when a child is being diagnosed. An article in the Sunday Times (June 2008) stated that, 'children are dying and being disabled because doctors in Britain take three times longer to diagnose a paediatric brain tumour than in countries including Poland and Mexico'.

Lung cancer is difficult to diagnose in its earliest and most treatable stages because of the limitations of present technology; the tumours are slow growing, but at the time of discovery is more rapid. Studies calculating the growth of lung tumours (based on mathematical models) suggest it takes 10-15 years from the appearance of the first cancer cell to detecting it by conventional chest radiograph. With faster growing tumours, a doubling of the bulk of the primary tumour, together with local and distant spread during the diagnosis, long delays in diagnosis are a negative factor in the patient's prognosis.

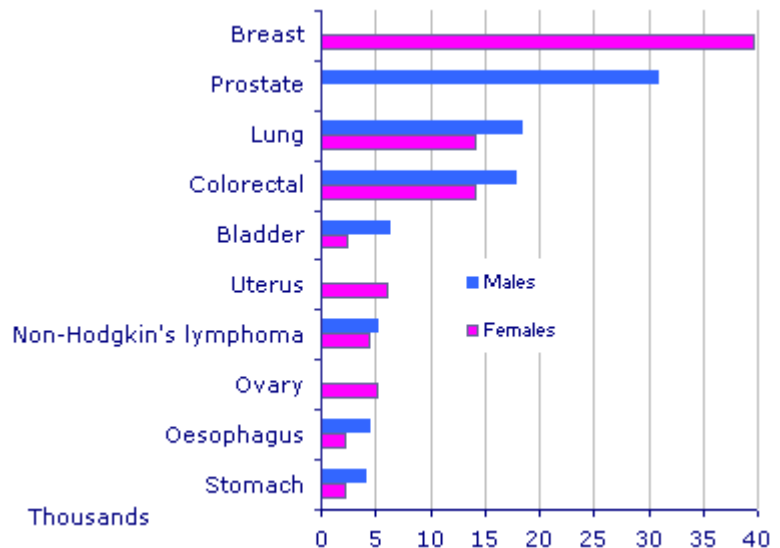


Figure 6: Incidence of major cancer strains – UK 2008

What is cancer?

Known medically as *Malignant Neoplasm*, cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues and spread to other parts of the body through the blood and lymph systems. Cancer is not just one disease, but many diseases. There are over 200 different types of cancer most named for the organ or type of cell in which they start.

It is mostly a disease of later life and more people in the UK are living to an older age. This means that the number of cancer cases that the GP sees will rise, and so the pressure to diagnose rapidly and accurately will intensify.

The main categories of cancer include:

- **Carcinoma** – cancer that begins in the skin or tissues that line or cover the internal organs
- **Sarcoma** – cancer that begins in the bone, cartilage, fat, muscle, blood vessels, or other connective supportive tissue.
- **Leukaemia** – Cancer that starts in the blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.
- **Lymphoma and Myeloma** – Cancers that begin in the cells of the immune system
- **Central Nervous system cancers** – Cancers that begin in the tissues of the brain and spinal cord.

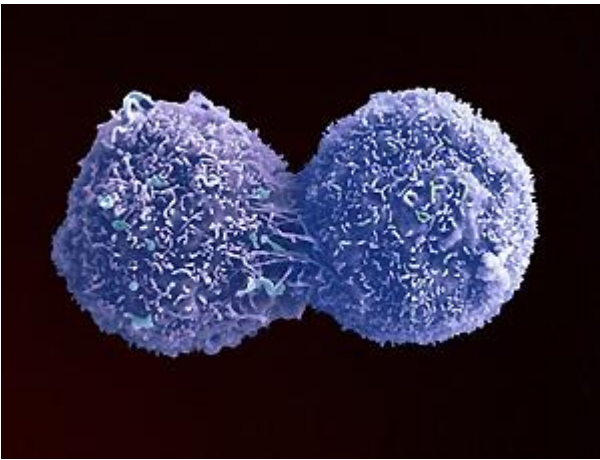


Figure 7: Lung Cancer Cell Dividing

Cancer can be detected or diagnosed at different stages during its development; the stages being indicated as I, II, III or IV or by terms such as localised, regional and distant.

Currently when a GP suspects cancer they might order x-rays and blood tests and recommend that the person visits an oncologist who will run other tests. These tests identify if cancer is present, the type of cancer and if it has spread to other parts of the body and the GP will decide the best way to treat it.

An oncologist or surgeon usually performs a biopsy. A piece of tissue is removed from a tumour or a place in the body where cancer is suspected and is examined under a microscope for cancer cells. Although at the present time it is considered the best way of examining a tumour, it can be a painful procedure and this technique is difficult or impossible to apply in the first stage of cancer. The sooner the cancer is found and the treatment begins, the better someone's chances are for a full recovery and cure.

The Role of Nanotechnology in the treatment of Cancer

Nanoshells are extremely small beads of glass coated with gold. Research has shown that Nanoshells injected into the body can seek out and bind to certain tumour cells. The small size of nanoparticles (10 to 100 nanometres) allows them to perfectly accumulate at tumour sites (because tumours lack an effective lymphatic drainage system). By irradiating the area of the tumour with infrared laser, it will pass through flesh without heating it. The gold is heated sufficiently to cause death to the cancer cells. Nanoshells can be targeted to be heated from the outside using a strong infra-red source.

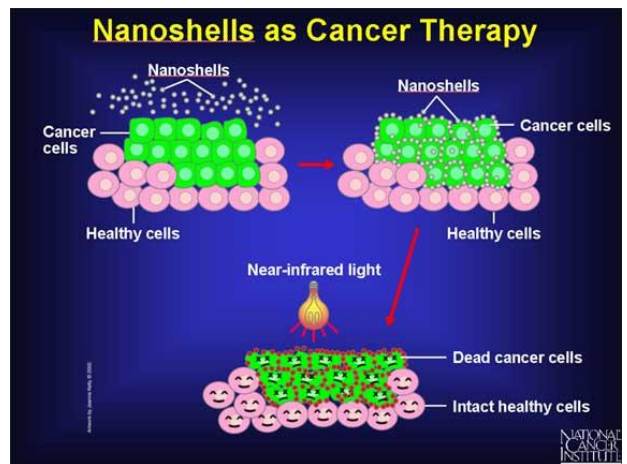


Figure 8: Nanoshells in Cancer Treatment

Such nanoshells could be made to deliver drug molecules at specific times by attaching it to a capsule made of heat sensitive polymer. The capsule would release its contents only when gentle heating of the attached nanoshell caused it to deform.

Cancers that appear predominantly at the body's surface, such as breast cancer or prostate cancer, would benefit from this process because the laser light would be most effective at this level. Nanoshells are more effective than quantum dots, as the main component of quantum

dots is cadmium which is toxic to the body. Nanoshells however contain gold which is proven to be biocompatible with the body.

Later research by Baker (2006) researched the use dendrimers in the treatment of cancer, its many hooks allowing it to attach to cells in the body.



By attaching folic acid to some of the hooks, folic acid being a vitamin, is received by the cells in the body. Cancer cells have more vitamin receptors than normal cells, so consequently Baker's vitamin-laden dendrimer will be absorbed by the cancer cell. To the rest of the hooks on the dendrimer, Baker places anti-cancer drugs that will be absorbed with the dendrimer into the cancer cell, thereby delivering the cancer drug to the cancer cell and nowhere else. Later research from Rice University (2010) has enabled pancreatic cancer cells to be killed with targeted gold nanoparticles.

Figure 9: Manmade Dendrimer with attached molecules used to deliver cancer fighting drugs

Nanobots

Nanobots are microscopic computerised robots that have components which are as small as 1nm in size. Different nanobots could be programmed to perform different tasks; to seek out and destroy the cancer, to 'inject' drugs into surrounding cells, and to enable a surgeon to watch the process by way of a nanoscale camera.

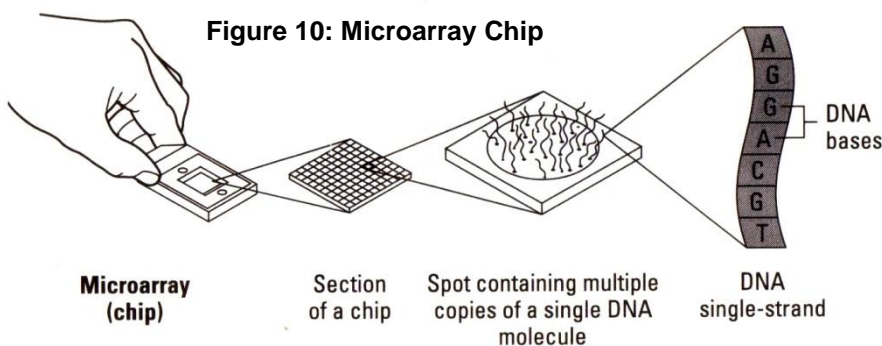
In the future, nanosystems such as cell repair machines may be able to enter cells, detect faulty components, and repair them.

Using nanotechnology to investigate possible methods of diagnosis of cancer using blood samples

Nanotechnology is an enabling technology that easily contributes to inexpensively extracting information from the body and transferring it to the GP and patient. The miniaturisation of nano devices for measurement and diagnosis has the potential to considerably reduce the mortality of cancer patients.

Lung cancer is the leading cause of cancer deaths worldwide. It is so deadly because of its tendency to spread or *metastasise* to distant sites in the body such as the liver and the brain. If the specific protein found in the blood and lungs of cancer patients could be identified at the early stage the chances of a patients' survival rate would dramatically increase.'

STM's and AFM's have enabled researchers to study DNA molecules and the genetic properties of cells and to detect cancer without a biopsy. One of the most important measures would be DNA; a DNA sequence could tell if a patient is vulnerable to certain types of diseases, and a microarray could be used to ascertain this.



Vulnerability to certain cancers is related to our genetic makeup. By studying genes in DNA, and identifying the proteins and antigens of different cancers sensors would need to be smaller, more sensitive, more selective, be integrated with

microelectronics and micro-fluids and be wireless in operation. Many cancer cells have a protein, known as epidermal growth factor receptor (EGFR) distributed widely on the outside of their cell membranes. Sensor chips containing thousands of nanowires could be used to detect these proteins and other biomarkers left behind by cancer cells. By using a combination of coating on groups of cantilevers, it would be possible to pick up the molecular signatures of particles. They would detect the presence of altered genes associated with cancer and diagnose the cancer type from the pattern of recognition. The prostate cancer antigen (PSA) could be reliably detected. Recent research has identified the protein *proepithelin* to be present in higher than normal levels in breast, ovarian, renal, brain and bladder cancers.

These small microprocessors could be interfaced into an electronic measurement system such as a computer. In the future, everyone could be bio-medically mapped for cancer and the likelihood of its development. However, some cancers such as myelocytic leukaemia are more challenging as future breakthroughs hinge on researchers obtaining greater knowledge of leukaemia stem cells that cause the disease.

To produce a micro-scanner enabling instant diagnosis of skin cancer

With further research, it may also be possible for a miniaturised high resolution AFM scanner. Because nanoshells possess highly favourable optical and chemical properties, could a scanning device be made possibly with 3D capabilities to scan under the skin's surface and to identify whether skin cancer is malignant or benign, thus performing an optical biopsy. This proposed device would be located in the GP's surgery for instant diagnosis.

Therapeutic implants to identify the progression of cancer, or the onset of secondary cancer in patients in remission.

If sensors could be implanted into high risk people, they could be continually monitored and GPs could be automatically alerted to any serious change. An increase in the levels of specific proteins and antigens present may help to predict when cancer is spreading.

The special properties that result from the nanoscale size of quantum dots, metal colloids, super magnetic iron-oxide and carbon based nanotubes would enable detection and treatment of diseases such as cancer to be treated biologically, that are both diagnostic and therapeutic in design. Could these special properties be miniaturised and adapted into sensors that besides detecting will also be triggered by the presence of cancer cells to release drugs to treat the cancer.

Personalised Health Monitoring

Medical nanotechnology- the integration of nano devices into communication and information processing systems could enable remote and personal health monitoring. Personal health monitors based upon adaptable, wearable and implantable wireless devices for clinical and ambulatory use, could provide improved patient health management everywhere, from the intensive care unit, to the patient's home, work and recreation environment. Sensors could measure blood pressure, pH, temperature, glucose and cell abnormalities that could detect cancer before the symptoms present. Widespread medical wireless devices could become an integrated concept; disease indicators made to a compatible standard, based upon mass-produced devices such as cell-phones. It could be possible to design a device modified as headwear to monitor serotonin levels in the brain (serotonin is a neurotransmitter that regulates mood). By monitoring serotonin, diagnosis and treatment of clinical depression will be quicker, and this technology could also be used to monitor other diseases such as Parkinson's disease and Schizophrenia.

The ability to monitor large numbers of physiological, biomedical, genetic and cellular systems simultaneously enables the human body to be studied as a dynamic network of biological, molecular, processes. This would consequently lead to *theranosis*, the tailoring of medicines to the individual, based upon continuous, detailed monitoring.

The information of each patient would be stored collectively. Looking at genes, proteins, or physiology measurement of a large number of parallel inputs and comparisons to support health, the data could be used to provide an accurate picture of the health of patients in a GP's practice or local area, or provide statistics for future research, which could eventually lead to the eradication of many diseases.

An example of how this technology could be put into practice

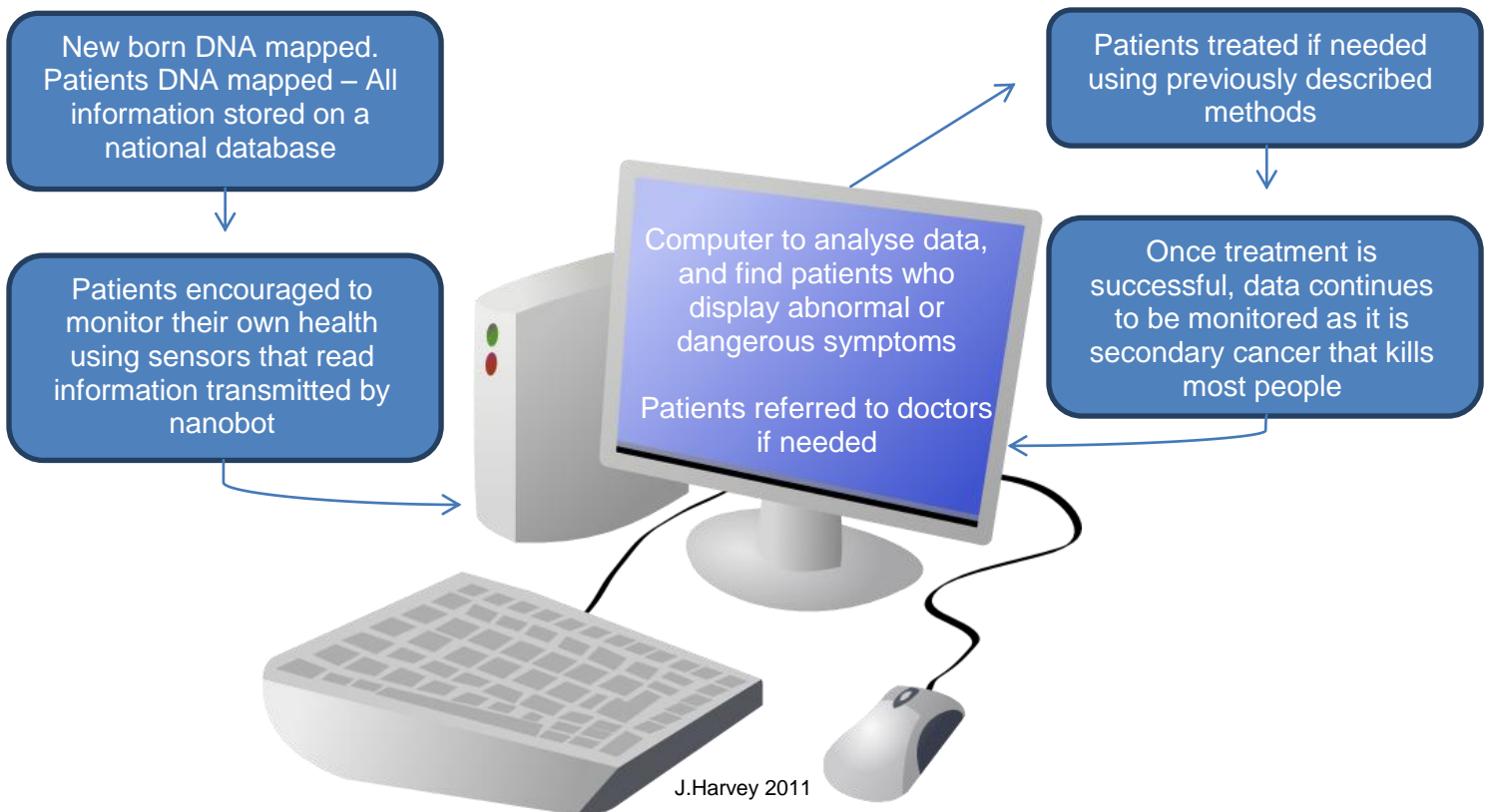


Figure 11: Exploring the possibility of Health Monitoring Systems

Such information may eventually lead to the development of an effective, personalised vaccine against cancer. Researchers of the University of Calgary (2010) have developed a vaccine based on nanotechnology which cured type one diabetes mellitus in mice. By developing an antigen-specific immunotherapeutic treatment, the damaged cancerous cells would be treated without harm to the immune cells.

The Ethics of Nanotechnology

Changes in the proteins due to the presence of nano particles in the bloodstream could trigger dangerous effects like blood clotting. The reaction of the general public towards nanotechnology and nanobots is not yet known, however there is a lot of speculation, particularly by scaremongering tabloids, of what could happen if this technology were to malfunction, or if it were to become autonomous.

When medical information is available wirelessly, there is also a need to ensure that sensitive information is protected from criminals and terrorists. The technology needed to make this information available wirelessly would have to be transmitted with very low range technology in order to ensure that the signals are not intercepted by those not meant to view them.

Also, certain religious and ethnic groups may not conform to these advances in medical science due to their beliefs, as some groups even decline blood transfusions.

Conclusion

Nanotechnology is not a 'standalone' scientific discipline, but rather a meeting point of traditional sciences like chemistry, physics, biology and materials science, a culmination of the required collective knowledge and expertise for the development of all technologies. It opens possibilities for more predictive and preventative treatments; new-born babies could have their DNA mapped, flagging up any potential problems, and showing the likelihood of them developing cancer. Providing medicine that is more personalised with emphasis upon greater individual participation in maintaining one's own health would therefore alter the patient/doctor relationship. Could it be possible that the prospect of self-monitoring and speedy diagnosis with portable testing kits be realised in the near future?

The knowledge of nanoparticles and their interaction with cells is still rapidly growing. As the progression of research in the area of biotechnology continues, new nanoparticles will continue to be discovered and new applications to medicine will be found which will in time equip the GP with diagnostic technology to enable the rapid diagnosis of all cancers.

The knowledge of today will become the breakthrough of tomorrow. Nanotechnology isn't just a fad – it's a euphoric scientific journey that offers potential medical breakthroughs that could eventually eradicate terrible diseases such as cancer.

References:

Figure 1: Nanoscale

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Figure 2: Buckminsterfullerene

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Figure 3: Quantum dots used to locate and kill cancer cells

<http://upload.wikimedia.org/wikipedia/commons/thumb/b/b2/MolecularImagingTherapy.jpg/400px-MolecularImagingTherapy.jpg>

Figure 4: Dimensions of a Carbon Nanotube

<http://jnm.snmjournals.org/cgi/content/full/48/7/1039/FIG1>

Figure 5: Multi-walled Carbon Nanotube

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Figure 6: Incidence of major cancer strains – UK 2008

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Figure 7: Lung Cancer cell dividing

<http://www.sciencedaily.com/releases/2007/03/070307153003.htm>

Figure 8: Nanoshells in Cancer Treatment

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Figure 9: Manmade dendrimer with attached molecules

<http://www.med.umich.edu/opm/newspage/images/nanocancerdendrimerlg.jpg>

Figure 10: Microarray Chip

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Figure 11: Exploring the possibilities of Health Monitoring Systems

Created by Jonathan Harvey

Computer image from:

<http://blogs.davenportlibrary.com/>

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Discussion

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