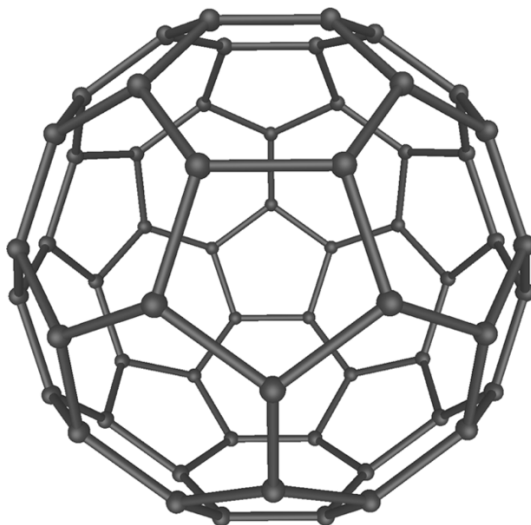


One Nano-Step for engineering; a Giant Leap for Medicine?
The Potential Developments and Ethical Controversies in
Nanomedicine



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PASS WITH MERIT

Research Paper
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ABSTRACT

During the 21st Century, research in Nanotechnology has become increasingly at the forefront of medical science. This paper explores the background to the ideas surrounding Nanotechnology, how they are already being applied to Medicine and current research. It will then offer potential developments: the use of graphene nanotubes as cancer diagnosis and treatment, Zeolite “cage” balls and blood glucose monitoring nanochips. However, the elusive nanoparticle has triggered concerns. We will investigate these health, environmental and social problems, and conclude the best way to deal with them.

INTRODUCTION

Nanotechnology is the branch of engineering involving particles smaller than 100 nanometres. [1] It has played an influential role in medicine already.

The measure “nano” is a billionth of a metre. From the Greek word meaning “midget”, Nanotechnology will allow us to build molecules and structures from individual atoms (bottom-up development) using an Atomic Force Microscope (with a platinum electrode of just 0.01nm), as opposed to “trimming down” molecules (top-down development). Essentially, the aim of nanotechnology is to try and mimic nature’s mechanisms by manipulating materials on an atomic scale. Scientists have been studying particles of this size for many centuries but its efficacy has been restricted by not being able to see the structure of nanoparticles until recently. [2]

First described by Richard Feynman, in 1986 Eric Drexler popularised molecular nanotechnology and proposed the idea of a nanoscale assembler able to build a copy of itself and other complex substances as stated in his work “Engines of Creation.” [1,3] Research is being carried out to employ this idea with healthy tissue engineering using “nanotubes” scaffolds.

In the 1990’s nanotechnology became increasingly eminent as Richard Fuller created the Buckminster fullerene balls also known as carbon-60. [4] This development led to nanotubes (fig 1), which can be used to construct nanotweezers, used to manipulate nanostructures prior to insertion in the body.

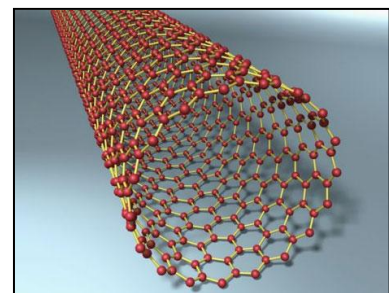


Fig. 1

Nanotechnology specifically relates to the cell structures of our body and due to likeness in size there are an abundant number of functions nanotechnology can be used to imitate.

One idea being researched is “nanobots,” that can be manoeuvred to carry out many functions inside and outside the body. This provides a gateway for operations that can’t be carried out using human skill, to be accomplished on a cellular level. Furthermore, there will be a reduction in human error and they can be programmed to create other nanobots, increasing cost efficiency.

Coronary heart disease is the biggest killer in the UK causing 275,000 heart attacks each year. [5] One option is to use nanodevices that would clean out the arteries helping to unclog those blocked by cholesterol fatty deposits. Furthermore, nanotechnology can be used

stimulate cell growth at the site of an artery where the lining has been weakened by the formation of an atheroma or thrombosis. This would prevent the weakened points from swelling up to form an aneurysm.

Nanotechnology has already featured in Diabetes research. Chandra Sharma has reported using nanoparticles to store insulin allowing them to pass through the intestinal wall into the bloodstream by means of two special coatings- one which attracts water and the other repelling water. When in the blood, the pH breaks the structure down releasing insulin. Trials have been carried out on rats and pigs, and have assisted in controlling these animals' blood sugar, thereby opening the avenue for human trials soon. [6] Nanotechnology can form nanocomposite contact lenses which change colour indicating blood sugar level. [7] Nanorobotic chromalloyocytes could actually carry out Chromosome Replacement Therapy (CRT) which would replace faulty DNA in Islet cells by inserting new chromatin into the nucleolus, enabling them to produce insulin. [8]

Nanomedicine offers us specificity in the administration of drugs via routes previously thought to be impossible, specifically proteins which are broken down by enzymes. The drug, including vaccines, can be encapsulated in a nanoparticle, allowing it to pass easily through the digestive system into the bloodstream, without injection (which carries a high risk of infection). The company BioDelivery Sciences has progressed to the Phase 1 human clinical trial stage for the drug "Cochleate"/ Amphotericin B which is held in a lipid crystal nanoparticle, used for treating fungal disease. Among the 48 volunteers, the Amphotericin B plasma concentration was measurable throughout the 14 day trial, proving the efficacy of the drug. Nanoparticle drugs also settle out of solution more slowly, thereby improving their formulation. [9]

Nanotechnology can provide advancements in medical diagnostics. For example bar code DNA assay techniques using magnetic nanoparticles can find faulty genes that cause hereditary diseases such as cystic fibrosis. Fluorescent semiconductor nanocrystals or Quantum Dots are a cluster of few dozen atoms which incandesce at certain wavelengths, acting as flexible fluorescent labels in the body. [10]

Applications in cancer diagnosis and highly targeted cancer treatment with minimal damage to healthy cells are being developed. Nanoscale cantilevers are built using lithographic techniques (fig. 2). They are coated with specific antibodies which bind to substances cancer cells

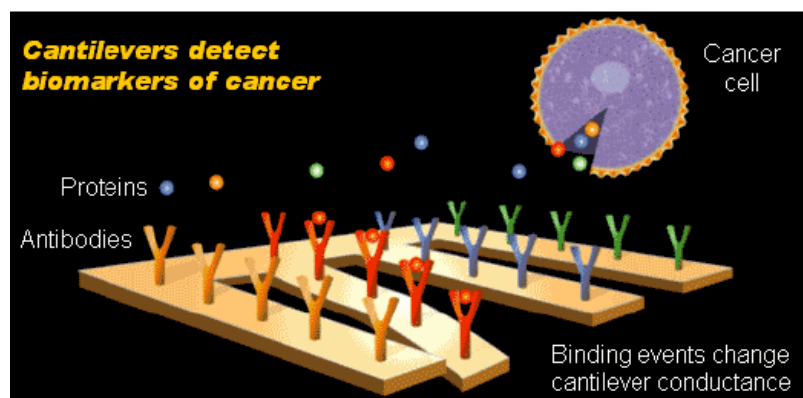


Fig. 2

secrete, thereby changing their physical properties which

can be detected. Quantum dots like cadmium selenide can be combined into specific monoclonal antibodies to create assays capable of measuring levels of microfibril proteins, nuclear antigens and the breast cancer marker Her-2. Nanoshell assisted photo-thermal therapy uses stable metal shells (usually gold), which preferentially concentrate in cancer

cells by “enhanced permeation retention”. They absorb light in the near infra-red region from a laser, heating up and killing the tumour tissue. Research has shown, the temperature rise using nanoshells is 30°C more compared to using laser alone. [11]

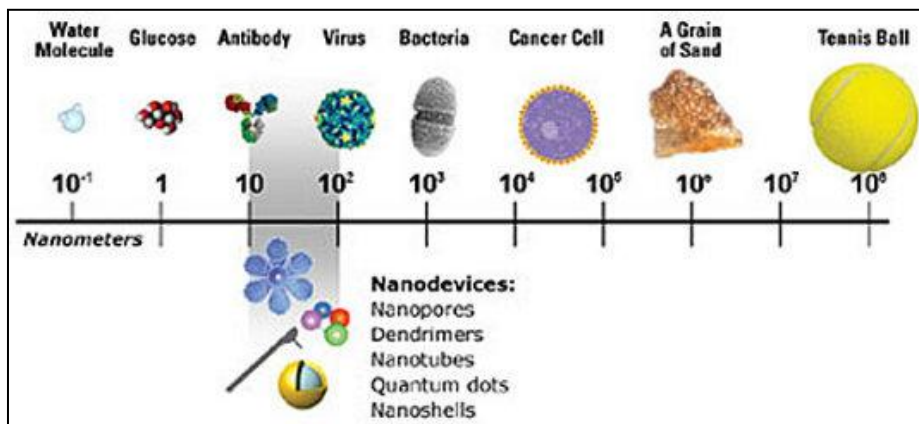


Fig. 3

Fig. 3 shows why nanoparticles are so effective: they can penetrate cancer cells, exclude pathogens, and encompass antibodies, leaving water and glucose concentrations unaffected.

DISCUSSION

The potential of the uses of nanotechnology Medicine are undeniably astounding, and could revolutionise the treatment of patients by tailoring treatment specific to the individual. This section will offer potential future developments based on the science already known, as well as possible ethical controversy regarding nanotechnology.

CANCER TREATMENT

With an ageing population and expansion of the economically developed world resulting in cancer causing behavioural changes cancer is rapidly becoming more prevalent. The number of global cancer deaths is expected to rise by 45% from 2007 to 2030. [12] With widely developing cancer research, Nanotechnology has the potential in the future to sensitively detect cancer, as well as give an indication to the type of cancer and treat it, simultaneously.

This could be achieved using nanoscale devices, based on the principle that devices smaller than 50nm could enter most cells, while those smaller than 20nm could transit out of blood vessels [11], thereby able to enter cells and organelles and recognise specific DNA molecules on a nanoscale. Transformation from a normal cell to a cancer cell could be caused by the over expression of normal oncogenes (which promote cell growth) and under expression or disabling of tumour suppressor genes (which inhibit cell growth). It could also be due to mutation in the genomic sequence of DNA, perhaps including insertion/deletion of “promoter genes” or the exchange of a small chromosomal locus. (See Fig. 4). These genetic changes cause “tumour markers” to develop on

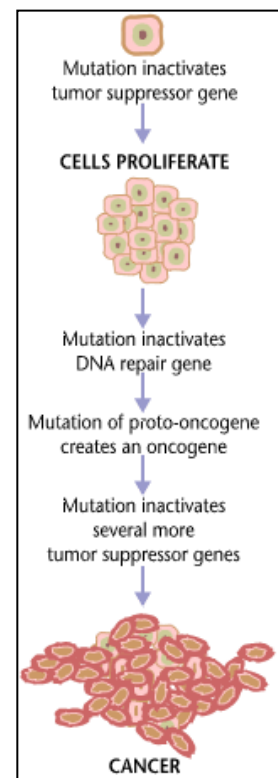


Fig. 4

cells, usually polysaccharides on the cell surface membrane. Proteins (e.g. HCG hormone) can also be made in much larger amounts by cancer cells, often in inappropriate places. [10]

Scientists at Princeton University have shown that single stranded DNA strongly interacts with graphene. We suggest investigating graphene nanotubes rather than carbon nanotubes as graphene is superconductive, very strong, has a huge surface area and is easier to make than carbon nanotubes. [13] If one strand of an oligonucleotide known to contribute to cancer's development (e.g. an oncogene) is covalently bound to the tube, when it enters a cancer cell, hybridisation between the target DNA sequence and the probe will occur and will be detected electrically. [11]

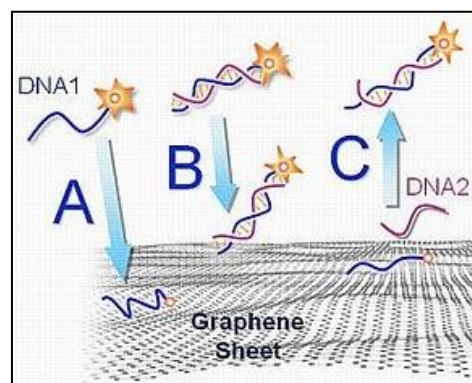


Fig. 5

Fig. 5 shows the interaction between graphene and DNA. Theoretically we think you could bind monoclonal antibodies to the tube complementary to the tumour marker polysaccharides or specific protein released. If this electrical signal is processed in a computer, it could pinpoint where exactly the nanotubes have aggregated in the body and the origin of the signal. Placing iron oxide inside these nanotubes would further enhance MRI imaging with its magnetic properties. Once having confirmed cancer is present and its location, we could use the extremely conductive properties of graphene to destroy cancer cells, with negligible damage to other cells as the graphene nanotubes locate specifically within cancer cells. Following recent research in the University of Colorado helping us to understand why DNA suddenly becomes super stretchy after a force of 65pn is applied [14], we can use this to understand how much energy is needed to break apart maliciously replicating DNA. Sending a small, sharp electrical current through the nanotubes could break the hydrogen bonds holding the two DNA strands together therefore halting the “interphase” period of rapid nuclear division.

Advantages of this type of treatment include the huge specificity of diagnosis, reducing the chance of misdiagnosis and the number of diagnostic tests needed to be taken. Used with MRI scans in conjunction, diagnosis of cancer lessens the need for PET and CT scans. As each scan can cost £1000 [18], and only shows regions of highly metabolic cells, MRI scans will be more cost effective and less invasive. Simultaneous diagnosis and treatment also reduces the need for drugs and radiotherapy and tumour regression without associated side effects. Living with a NHS with a severe budget limit, Cancer cost the UK £18.33 billion in 2008, and this is expected to increase to £24.72 billion by 2020 [15]- if proven successful (after clinical trials), this could reduce the cost.

ZEOLITES

Zeolites are essentially “molecular sieves”. They are naturally occurring, crystalline solids, usually containing oxygen, silicon or aluminium in the framework. The characteristic feature is their well defined structure, where tetrahedra (silicon atoms in the centre surrounded by 4 oxygen atoms) link by their corners forming cages, cavities or channels,

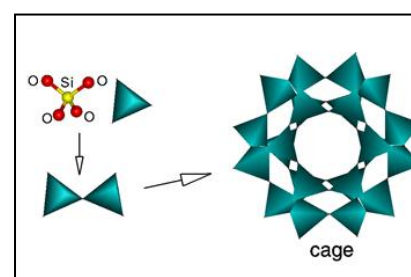


Fig.6

shown in fig. 6.

The key feature is that some have nanopores (typically with a limiting pore size of 0.3 to 1 nm in diameter), allowing them to preferentially adsorb some molecules and exclude others. [16] There is currently a lot of RND invested into the exploitation of the uses of nanoporous Zeolites (see the British Zeolite Association). Presently, they have principal uses in petrochemical chemical and water softening, however we feel could have novel uses in the body. Via nanostructuring using an Atomic Force Microscope the Zeolite cage could be formed into a “buckyball” type nano-sized feature. When in the bloodstream, as Zeolites tend to have overall negative charge they attract positive metal ions, but have a tendency to adsorb heavy metal ions through their pores (which are more charge dense and more strongly held in the structure). [17] Therefore the digestive system and nervous system would remain unaffected as sodium and potassium ion concentration would also be unaffected. Free radicals, with unpaired electrons are also attracted to the structures, and could react with antioxidants such as Melatonin placed in the balls, thereby eliminating free radicals. The general nanoporous structure would be based around the lipid bilayer, which also has protein pores allowing metal ions and water soluble substances to be absorbed.

Considering both high heavy metal (particularly cadmium, mercury, aluminium and lead) and free radical concentration in the blood have been linked to increased risk of cancer, with heavy metal concentration being linked to autism also, it could be used as a preventative treatment. In an investigation regarding Autism in relation to the distribution of hazardous metals in San Francisco, there was a moderate correlation between incidence and estimated airborne metal levels at birth (notably mercury, cadmium and nickel), and mercury and lead are known neurotoxins and potential endocrine disruptors. [18] We envisage it being particularly useful to those with metal implants, which could irritate adjacent tissue carrying an increased cancer risk. As the surface area of nanoparticles are so large and treatment would be hugely effective. Regarding the free radical reaction, the nanoparticles would focus the reaction in one area, purposefully adsorbing free radicals, favouring this treatment over simply taking antioxidant tablets. Another advantage is that they could be taken via a nasal spray, as the molecules are small enough to pass across membranes into the blood, as well as tablets.

DIABETES

Poor blood sugar control as a result of the autoimmune destruction of insulin producing beta cells in the Islets of Langerhans in the pancreas is known as Type 1 Diabetes. It is fatal unless treated with regular insulin injections to control blood sugar, which can be a great burden. 40% of the 135 million Diabetes sufferers must inject themselves on a daily basis and complications can result from poor blood sugar control such as hypoglycaemia and hyperglycaemia. [6] The ideal cure for Type 1 Diabetes would be a method to continually monitor blood glucose levels and release insulin accordingly- effectively taking over the pancreas function. Obviously pancreas transplantation is a possibility and Islet cell transplantation is undergoing major research, proving to be less invasive. However the immune system will attack the foreign cells in these methods, and immunosuppressant drugs must be taken in the long term.

As Diabetes is malfunction on cellular level, we believe nanorobotics has huge potential in actually carrying out homeostasis of blood sugar. Nanotechnology has already featured in Diabetes research. However, current nanorobotics developments (such as CRT) require knowledge of non-existent advanced medical nanotechnology, and so are far less accessible. We propose using nanochips and storage nanobots to actually remain in the body and carry out the function of the pancreas via computerised negative feedback systems.

A nanochip implanted in your body could theoretically monitor your blood sugar level, sending feedback to a small computer which the person carries. Having knowledge of the time of day, and the diet of the individual, the computer will determine whether the blood glucose concentration is too high or too low. If it is too high then the computer sends a different signal to nanobots circulating in the blood, which store insulin, to release more insulin. If too low, the signal would be sent to reduce insulin output. Eventually, detailed engineering may create nanobots which carry out processes being discussed now, such as onboard computation, navigation and power communication. Detection of blood sugar concentration by a nanochip, communication with a computer and release of insulin may all be able to take place in one nanobot. Fig. 7 shows a realistic model of a complex nanobot which could be used for CRT or Insulin monitoring.

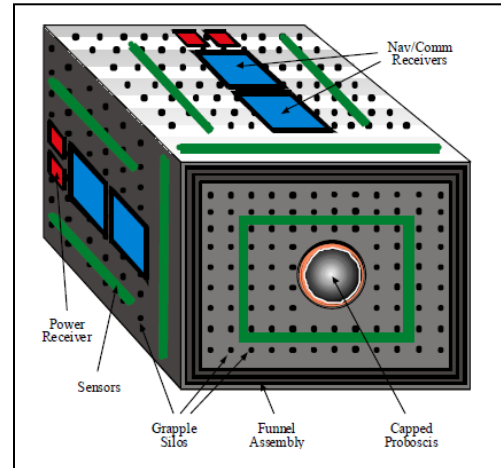


Fig.7

The obvious advantage is more constant blood sugar levels, as opposed to “peaks and troughs” experienced with injection (see fig. 8), simulating a natural bodily process. Being nano-sized, the small devices will escape the guard of our immune system, eliminating aggressive immune response. However, there would need to be a way of the nanobot disintegrating or leaving the bloodstream after having emptied all its insulin.

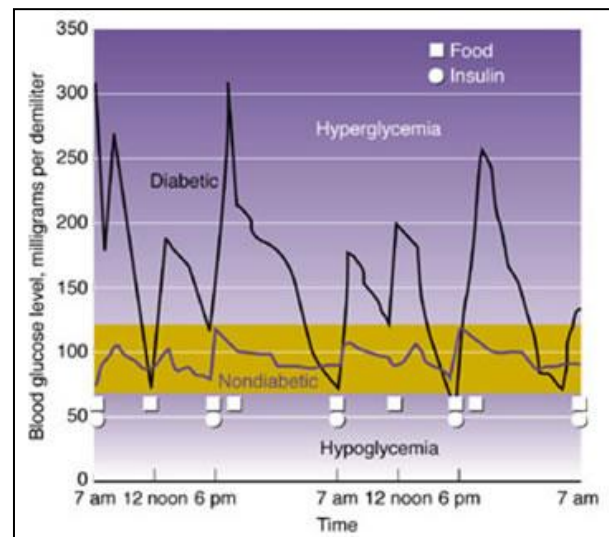


Fig.8

Other potential developments could include using nanostructuring to create hip replacements, using metal or actually structuring calcium and phosphates (also known as biomineralisation). These structures would be extremely strong but very light (carbon nanotubes are 100 times stronger than steel, yet one sixth the weight). Nanostructuring using atomic force microscopes will make it possible to structure nanomolecules using

Rational Drug Design with such specificity they could be ingested into the body and act as competitive inhibitors to dangerous enzyme catalysed reactions. Zeolite based plasters for wounds could contain nanopores large enough for oxygen to pass through (one molecule just 292 pm), but small enough to exclude pathogens. These plasters could contain antibacterial agents in nano-capsules with “receptors” on the surface complementary to certain enzymes which would break down the capsule to release the medicine.

ETHICS

With the exciting potential of Nanotechnology to transform medicine, it is easy to oversee negative aspects. Realistically, nanotechnology is still a fledgling development and more involved ideas need to undergo clinical trials and analysis to evaluate their impacts on health, society and the environment.

INSIDE THE BODY

The miniaturisation of particles to nanoscale has revealed uncharacterised, dangerous properties.

The nanoparticles titanium oxide and zinc oxide are currently used in well over 300 sunscreen products in today’s market, to reduce the visibility of creams. However concerns have already been raised on potential dangers to the body. When particles are reduced to nanoscale, their physical and chemical properties can be transformed as a result of an increased surface area to volume ratio. The scientist Amanda Barnard has shown that they can induce the formation of free radicals in UV light, via a photochemical reaction, which can damage DNA in cells [19, 20]. More worryingly, recent studies have shown if zinc oxide nanoparticles are ingested, they are twice as toxic to colon cells compared to normal sized particles, increasing the risk of colon cancer. [21]

When nanoparticles are in the body, their extreme reactivity can cause damage to surrounding tissues. Non-biodegradable nanoparticles with specific coatings, allow them to be selectively disposed and accumulate in certain organs, such as the liver, potentially causing harm. Nanoparticles are small enough to cross the blood brain barrier, which is virtually impenetrable to most proteins. Nanoparticles not intended to reach the vulnerable brain, may cause unintentional serious damage. These dangers are further amplified as nanoparticles are small enough to evade the immune system which usually attacks exogenous substances. Specialised phagocytes (macrophages) would ordinarily engulf non-self material, but cannot detect particles smaller than 200nm, thereby allowing nanoparticles to circulate. [11] These particles may enter the cell membrane pores interfering with cell functions like motility and removing bacteria.

Complex nanoparticle treatment research is still in its infancy, and thorough clinical trials in vitro and in vivo are needed to analyse the interaction of nanoparticles with bodily systems, and the minimum dosage required to cause harm.

SOCIAL

Nanomedicine could prospectively improve healthcare for treatments of a variety of diseases, however this will come at a steep price. If nanotechnology treatment was introduced into the healthcare market, would increased efficiency bring down overall healthcare costs or manufacturing costs increase them? If they do increase, it is highly likely that the social healthcare gap between rich and poor will widen, especially in countries with privatised healthcare (e.g. USA). In the UK, it may exacerbate the healthcare divide between the industrial north and affluent south. Additionally, globally we are facing the threat of an ageing population, and with the potential of nanotechnology people could live even longer. Will savings in efficacy of treatment finance increased health expenditure from demands of the elderly?

CONCLUSION

We believe that our thoughts could target the some of the most expensive and debilitating diseases, saving money and lives.

By using graphene nanotubes we can specifically target the DNA of malignant cells, without damaging healthy cells. Simultaneous diagnosis and treatment saves huge costs to the NHS by preventing 2nd malignancies due to the high effectiveness of the treatment, and reducing the need for assisting drugs or radiotherapy. Nanoporous zeolites can trap free radicals and toxic heavy metals in its structure, potentially providing increased defence against cancer and autism. As they are small enough to pass membranes into the blood, they can be given as a nasal spray- more “child friendly”. Zeolite plasters for wounds could even selectively exclude pathogens, reducing healing time. We also propose that nanochips could be implanted into diabetic patients to monitor blood sugar levels, and via a computerised negative feedback loop, another message can be sent to insulin storing nanobots to release insulin. It will end the era of blood pricking and injections, as well as improving glucose homeostasis, thereby reducing stress to the patient.

However, stringent clinical trials are needed to evaluate the effect of nanoparticle treatments in health and the environment, following concerns that they could be toxic to humans and could aggregate in the environment. Therefore, the success of nanotechnology will be determined by balancing benefits against risks. Nanomedicine treatments should only be implemented on a wider scale until it is proven that benefits to health outweigh the risks to the body and environment. Strong analysis of how it will modify distribution and quality of healthcare to ensure it is as fair as possible is also needed. We must take these discerning clinical trials very seriously and they must be strongly regulated to ensure the desires of scientists or pharmaceutical companies do not make results invalid/biased. Although we think nanoparticles should be treated as dangerous until proven that potential benefits can outweigh risks, this should only fuel research into Nanomedicine further, particularly into nanobots which can carry out cellular procedures such as CRT or insulin control. For we believe that nanotechnology is able to revolutionise the treatment of patients globally, by improving efficiency and specificity: nanotechnology definitely has the potential to be the greatest leap Medicine has ever seen.

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Pictures

Fig. 1: Carbon Nanotubes

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Fig. 2: [11]

Fig. 3: Building the future one nanoparticle at a time

<http://www.theismaili.org/cms/317/Building-the-future-one-nanoparticle-at-a-time>

Fig. 4: Cancer

<http://en.wikipedia.org/wiki/Cancer> - courtesy of NIH

Fig. 5: [16] Image credit to Pacific Northwest National Laboratory

Fig. 6: [19]

Fig. 7: [10]

Fig 8: What is Diabetes?

<http://www.trustyguides.com/diabetes1.html>

Fig 9: [15]