The Dendrimer Revolution of Nanotechnology
And the Ethics behind a Nano-Future

BY

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PASS WITH DISTINCTION

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2007

Abstract

Nanotechnology a discovery that could be the next great step for the development of human life as we know it, as important as the discovery of gravity by Sir Isaac Newton or of electricity by William Gilbert, two things that we take for granted today.

As the debate continues for what the application of nanotechnology should be especially the dendrimer technology in the medical field, I will be looking at some of the future developments that dendrimers could give to fight disease. With the potential to give significant health benefits and improve quality of life to people all over the world this subject needs to be fully understood and researched to ensure no unnecessary risks are taken.

Introduction

History

In 1959 Richard Feynman was the first scientist to talk of the manipulation of atoms to fabricate materials to atomic specifications, declaring "The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom[1]."The pioneering thought almost ignored until in 1981, until Eric Drexler produced the first scientific paper on the subject capturing the potential and the imagination needed to develop the nano-thought further. In the following decades of the 20th century the field of nanotechnology was born with Drexler considered its forefather co-founding the Foresight Institute that has guided the technological advancements and ethics of the field to the present day. Engineers were able to build machines and structures from the "bottom up" instead of simply miniaturizing current technologies of the time. Although progress was hampered through out, as the size of nanoparticles and scientists ability to see what they were working with was a problem. It wasn't until the development of powerful microscopes in the late 20th and early 21st century that has lead to a revelation in the field, with future applications and uses of nanotechnologies only having their surface scratched.

Understanding Nanotechnology

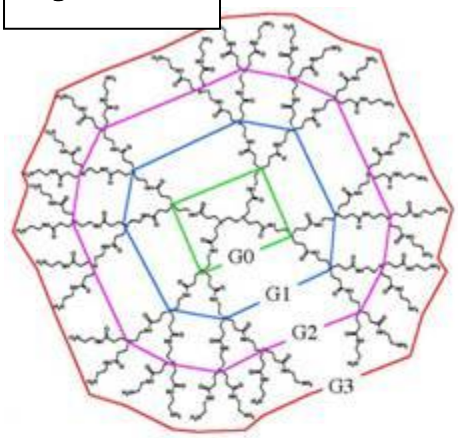
The principle thought behind nanotechnology is that instead of continuously miniaturizing structures by chopping parts off, "there is plenty of room at the bottom" allowing for structures to be built from the manipulation of atoms "at the bottom" to fabricate materials. The thought is that with this technology the manipulation of the physical world through its base component (atoms) will be much the same as how computers manipulate the digital world through binary code. As it is not one type of atom makes a specific object. Instead it is the arrangement and different combinations of atoms that determines the properties, uses and essentially what it will be. For example a carbon and oxygen atom combined creates a gas that circulates in the atmosphere and is produced as a bi-product of respiration in the body. Rearrange these to form a different structure in addition with a few other elements and with the same atoms a human being itself is formed[3]. A definition of nanotechnology is "a branch of engineering that deals with the design and manufacture of extremely small electronic circuits and mechanical devices built at the molecular level of matter, that are man-made[17]." With figure 1 showing some of the applications made by commercial companies already.

Figure 1 [16]

Company	Product
CytImmune	Gold nanoparticles for targeted delivery of drugs to tumors
Nucryst	Antimicrobial wound dressings using silver nanocrystals
Nanobiotix	Nanoparticles for targeted delivery of drugs to diseased cells
Oxonica	Disease identification using gold nanoparticles (nanotags)
Nanotherapeutics	Nanoparticles for improving the performance of drug delivery by oral, inhaled or nasal methods
NanoBio	Antimicrobial nanoemulsions for nasal delivery to fight viruses (such as the flu and colds) and bacteria
Novavax	Drug delivery through the skin using micellar nanoparticles and oral drug delivery with propriety structures called Novasomes
BioDelivery Sciences	Targeted oral drug delivery to diseased cells using a nanocrystalline structure called a cochleate

[16]

Figure 2 [8]



As can be seen one of the main ideas being invested in, is the nanoparticle popping up in 5 out of 8 companies listed. The nanoparticle being a dendrimer, structured like a tree, has a branched polymer structure synthesized by monomers over generations. Synthetic control is key to making the structure using step-wise reactions and purification to control the size, architecture, functionality and monodispersity. Figure 2 shows the structure of a 3rd generation polyamidoamine[8]. This part of nanotechnology is what I will be specifically looking at, as dendrimers could lead to major breakthroughs in the medical field for a large number of conditions.

As nanotechnology sees scientists copying nature at fabricating organic structures on the nano scale, the template that is provided by nature in front of human kind is a perfect reference point at which to start from. With the smaller the particle used, the better the result for tissue growth and regeneration. As the same point is being researched by the use of stem cells, which have the ability to turn into other specialised cell types as they are taken at an early stage of development. The three main types being embryonic stem cells (totipotent) with the ability to turn into any tissue, adult stem cells (multipotent) which are bone marrow cells capable of producing blood cells, and umbilical cord stem cells another type of multipotent cell. Figure 3 shows when stem cells of different variants are taken from an embryo, infant or adult.

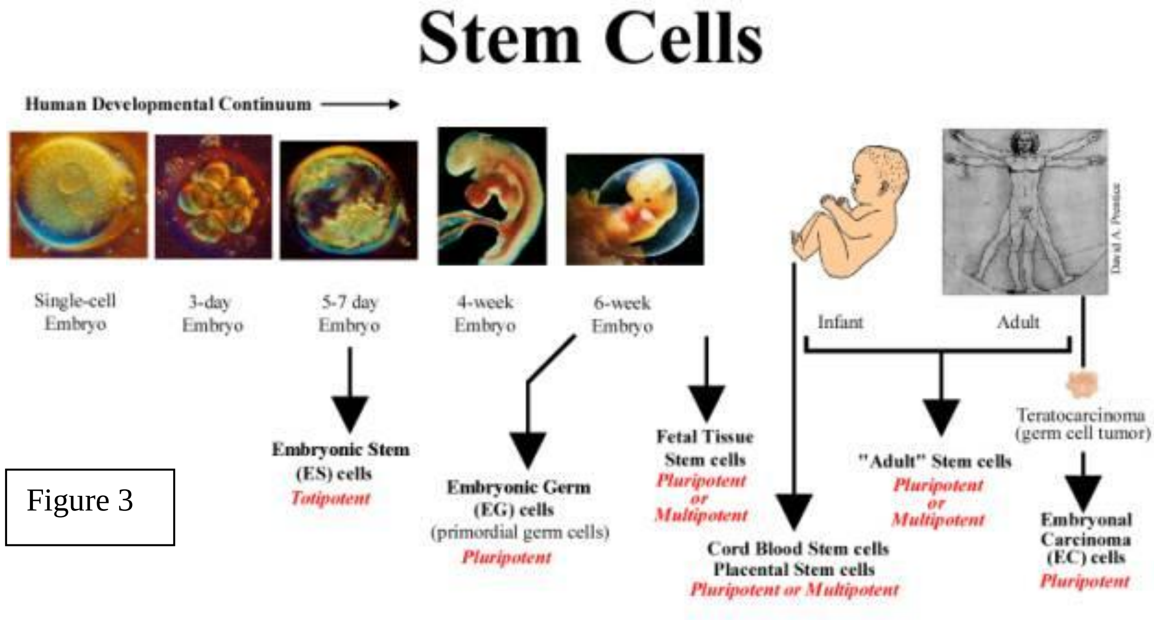


Figure 3

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As the potential for both stem cells and nanotechnology is the same with the ability to improve tissue growth and regeneration as well as finding cures to major diseases such as diabetes, brain diseases, Parkinson's and cancer. By combining the technology of the dendrimer and embryonic stem cells, the stem cells could be effectively delivered by the nanoparticles to specific parts of the body for the treatment of conditions with the cells turning into any type of tissue needed. This technique is being researched by Thomas J. Webster at the Brown University in Providence, and by colleagues at Yonsei University in Seoul, to treat brain damage conditions of Parkinson's, Alzheimer's and other neurological disorders. By combining stem cells with nanoparticles and putting them into brain damaged rats they found that the stem cells stayed in the damaged parts of the brain and even started to differentiate into functioning neurons. Whilst when both were applied alone, no effects were shown as stem cells went to healthy parts of the brain where they were not needed. With nothing shown over the eight week period it was clear that the potential for the combined technologies was immense whilst their individual application was not effective in this case[18].

As size is important, the nanotechnology operated is anything below the micro level, with it hard to pinpoint the exact size of something when referred to as nanotechnology; it can range normally from 1nm to 100nm in size. With a hair measuring the size of approximately 80,000nm it is quite hard to imagine how small this technology actually works at. However in the future devices could become even smaller as the rigidity of the definition of its size is in question. Demonstrated in figure 4, the scale of how man made and natural things compare with nanotechnology.

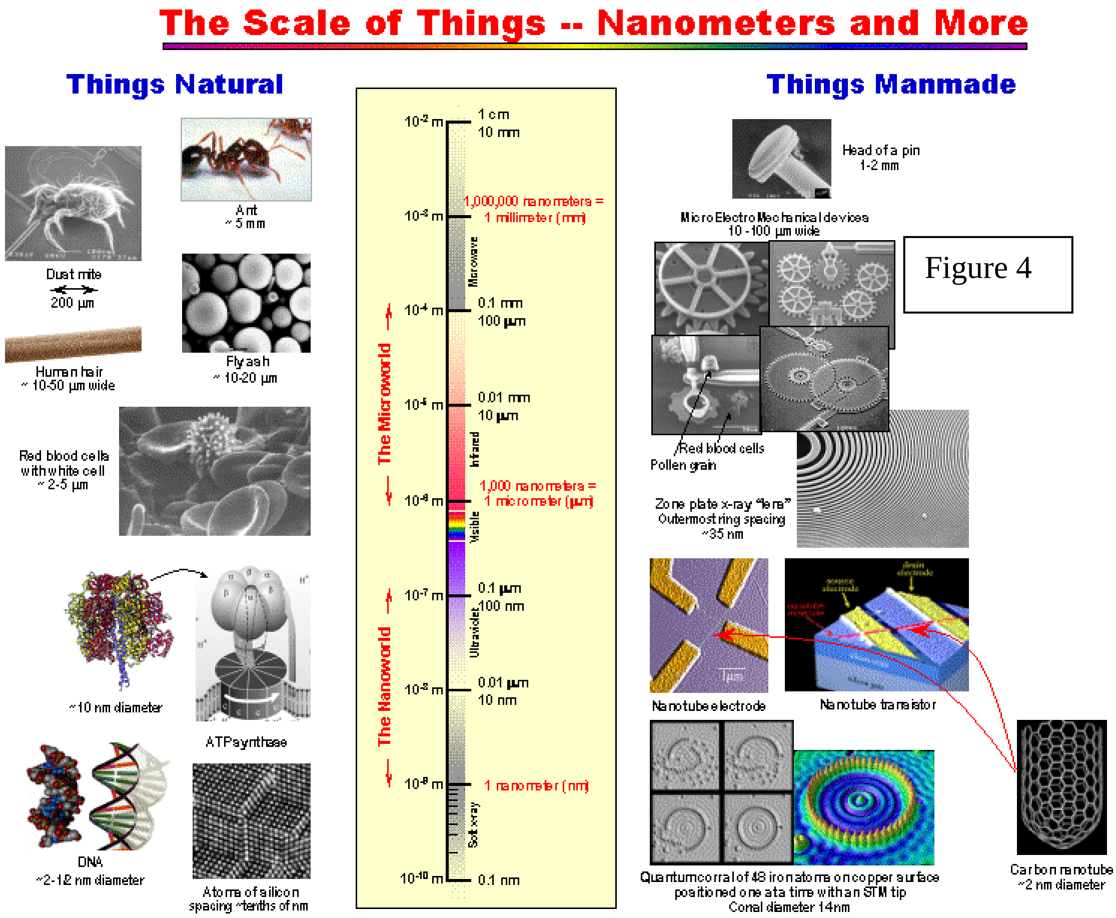


Figure 4

[20]

Discussion

Cancer

Cancer is one of the most heavily feared diseases in the world with the American Cancer Society estimating that 7.6 million people in 2007 died worldwide from the disease[7]. Cancer medically being a malignant neoplasm, which can be described as a group of cells having the traits of uncontrollable growth, capable of invasion of other cells through intrusion and destruction of adjacent tissues. With a possibility of metastasis, that is the spreading of cancer around the body through lymph or blood. These three key characteristics make a cancer malignant in comparison to its counterpart a benign tumour that is self-contained, unable to invade or metastasize. Apart from in cases such as Leukaemia where no tumour is formed, cancer operates at the cellular level to contaminate cells.

Treatment of cancer is possible through chemotherapy, which is the application of anticancer drugs to the body. These drugs have serious side effects that are well known in public knowledge as hair loss, nausea and fatigue, with some rare cases causing death[9]. This is where nanotechnology is helping to pioneer new ways of administering the drugs to the body. As in essence a device could have a small computer, sites on the molecule to determine the concentration of other specific molecules, with a supply of some poison included which could be released by recognizing the characteristics of cancerous cells for the nanodevice to kill[10]. By directly attacking specific cancer cells instead of pumping drugs around the whole of the body that can affect healthy cells the side effects of the drugs can be minimized, with the effectiveness of the drugs on reducing and completely eradicating the tumour increasing significantly due to the direct application of the drug. The technology referred to, known as nanoparticles is being implemented in the cancer field now, the nanoparticle a type of dendrimer, a branched molecule that can easily have different type molecules fitted to its outer surface to allow it to perform different tasks. The dendrimer can have 12 sites at which molecules can be attached to it, allowing it 12 different functions. The nanoparticles made of biodegradable polymers such as poly(d,l-lactic-co-glycolic acid) and poly(ethylene glycol)[11] encapsulate the chemo drug, so when coming into contact with cancer cells the particles dissolve, releasing the drug directly into the cell.

The nanoparticles can find the cancerous cells due to RNA strands attached to them, these RNA strands known as aptamers, bind to specific proteins that are found in the cancer cells[11].

The nanoparticles are able to reach tumours as the tumour itself requires blood vessels to sustain itself (angiogenesis); the blood vessels provide a direct pathway to the tumour for the drug to be administered. As demonstrated with figure 5 the nanoparticle can be less than 5nm thick and easily capable of circulating through the blood stream without trouble.

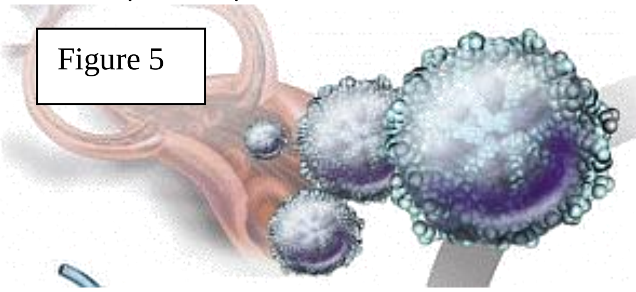


Figure 5

By using this technology different kinds of cancer with different protein markers can be specifically targeted. The use of the nanoparticle does not have to stop there either, as with different RNA strands able to be attached to these dendrimer type structures, they are able to search and find various targets with specific protein structures, administering different drugs for specifically recognized diseases, not only cancer. Not always trying to destroy the cells they could also be used to release dyes into the cells as a contrasting agent[8], along with the capability of being fitted with different nanomolecules able to analyze the blood and the affects that drugs have on the body. The possibility of this particle being developed in the future maybe not to just target disease but to target fat cells within the body to fight obesity, or the possibility of the particles delivering electronic impulses to the body, giving a paralyzed patient the ability to regain movement through combining the delivered impulses with other nanotechnologies that can bypass damaged nerves and communicate the pulses to each other from the brain.

The potential for the nanoparticle is almost immeasurable as its versatility is a great asset, but in the near future it could become the essential delivery system for administration of drugs, dyes, hormones and other chemicals to the human body, with the need for a more reliable and effective way to combat deadly diseases this form of nanotechnology could potentially give a patient a new lease of life. Research at the University of Michigan by Jolanta Kukowska-Latallo has shown, by administering the chemotherapy drug methotrexate in nanoparticles to mice with cancer. That 30-40% of the mice given the nanoparticle in the 99 day test, a 30 day tumour delay had occurred, the equivalent to an extra three years for a cancer patient[21].

Obesity

Obesity is one of the quickest growing health problems in developed countries, causing around 30,000 deaths a year in the UK alone. Scientists predict that adult obesity will be out of control, as it has almost quadrupled in the last 25 years. Obesity is of a major concern with 22% of Britons obese and three-quarters overweight, costing the NHS £500 million a year[4]. Obesity can cause several health problems - hypertension, liver disease, type two diabetes, hyperlipidaemia, immobility, falls and eventual heart disease, along with obvious psychological effects and the chance of increased injury.

Through the use of nanotechnology a huge step can be taken to tackle obesity at its source. The source being the food eaten and the life style that people live today in the modern world, as preventing the disease is just as important to curing the condition once obtained.

It has already been documented that nanotechnology can be used in fluidics-based devices to detect and manipulate single-cells and single-molecules. With real-time monitoring and fluorescence measurement these lab-on-a-chip devices could replace amniocentesis with a non-invasive blood test[5]. This example of a diagnostic tool, the dendrimer structure that can be fitted to carry out various tasks could be used in conjunction with other nanotechnologies to not just test blood, but to test the contents of the stomach at digestion.

Through real-time monitoring of the breakdown and digestion of food in the stomach nanotechnology could be used to detect increased levels of harmful toxins, proteins, carbohydrates, minerals and fats such as trans-saturated fats that it has been programmed to recognize. As digestion is basically a process of breaking down big food particles into individual molecules, tiny enough to squeeze through the intestinal lining into the bloodstream. The computer programmed nanotechnology would be able to recognize the chemicals and excessive amounts of molecules in people's diets and successfully monitor and if necessary remove them. Removing the excessive molecules can be done by creating nanomechanical devices capable of trapping them and then after binding with other nanodevices with trapped molecules inside them, to be safely removed from the body. The use of nanotechnology at the molecular level by recognising and trapping unwanted excess amounts of molecules prevents the molecules themselves from being absorbed into the blood stream, for example excessive carbohydrate absorbed through the wall of the duodenum would not be burned within the body for energy[6] instead it would be stored creating fatty build ups that can in large quantities over time cause obesity. By making sure vast quantities do not reach the stage to be absorbed in the small intestine, the likelihood of obesity can be cut drastically. By binding the nanodevices after trapping has occurred, small pellets of nanodevices joined together can be flushed out of the bowels with the waste, the binding together of the nanotechnological devices would prevent them from being absorbed into the blood and would allow for the waste molecules to be removed from the body immediately. The nanotechnological devices could be taken in a capsule form so that once ingested the capsule would dissolve and allow the nanodevices to get to work in the stomach.

This could be implemented as a heterogeneous molecular nanosystem capable of having each individual device to do its tasks in the overall process, such as the conducting of highly analytical measurements through processing microliter and nanoliter volumes, or by using a dendrimer type molecule to attach other molecules capable of binding to the molecules to trap them[8]. As microfluidic technologies can fabricate highly integrated devices to perform several different tasks on the same substrate chip, with techniques relatively inexpensive to produce the nanodevices on a mass scale. This would successfully help to prevent and cure obesity by removing excess amount of molecules in the stomach and before adsorption through the small intestine, its potential to also recognise toxins and remove them before ingestion and damage can occur would be a considerable benefit.

Although, this level of nanotechnology would only occur in 4th generation nanotechnologies[2] that could not be available in the foreseeable future for some time, the main drawback of these technologies being the ethical dilemmas of the implications of them.

Ethics of Nanotechnology

As the field of nanotechnology widens and the potential for good and bad become apparent, order needs to be established and the ethical dilemmas of this technology will have to be understood fully to ensure that the bad doesn't outweigh the good in the foreseeable future.

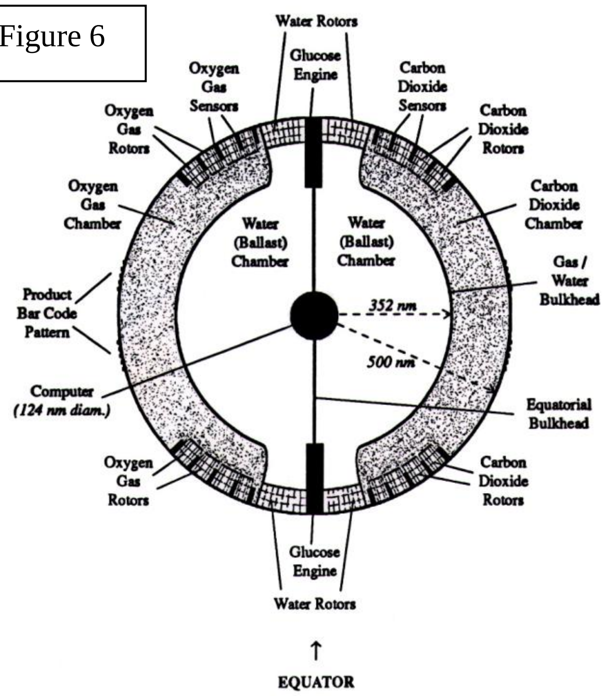
Damage

With recent study showing that nanoparticles were able to be absorbed by the livers of research animals, with brain damage being caused in some fish exposed to the particles within 48 hours<12>. These facts are worrying as this proves that with the increased health benefits that nanotechnology can provide there is also a greater risk for the human body to respond to this foreign particle introduced into the system. Should scientists be introducing man made machines into a biological system that runs in equilibrium, where a slight technical difficulty could potentially upset this balance and cause the body to crash? With the possibility of nanoparticles (the dendrimer) in question, should researchers be taking the role of god on? These are some of the most worrying questions that will be of major concern in the field of nanotechnology as it expands and gains more support to become the 1 trillion dollar business<12> that is expected.

The wrong message

As steroids and other drugs have provided a significant advantage over the years in developing and strengthening the human body particularly in sport, nanotechnology and especially nanoparticles could see this taken to an even higher level. The influence of sport on thought processes of the public and the viewing of what is right and wrong can play a major role, with the basis of fair play and sportsmanship a key aspect always reinforced, younger generations could see fit to cheat and use drugs. With nanoparticles ability to administer drugs to specific cells and parts of the body the application of these drugs to muscles and the brain for example could see people with increased physiological performance and potentially increased psychological performance. This could pose a completely new way to cheat as the drugs wouldn't be necessarily circulating in the blood, but injected straight into the intended cell for performance enhancement. An example being the already predesigned

Figure 6



"respirocyte", an artificial version of a red blood cell, capable of providing oxygen to the body through a store in its structure, shown in figure 6. This could allow a heart attack victim to breath for another hour, allowing them to get treatment, or in a normal person this could give them a significant advantage, being able to work their body harder[13].

The technology being utilized for medical conditions could save many lives, but at the same time the use of the drug as an enhancer could send the wrong message to people. Seeing fit to use drugs to make them feel better and enhance their physiological and psychological state. If a drug or type of enhancer (the nanoparticle containing a drug) is made legal and is accepted in the community, what does this say about other drugs that people could argue can provide benefits, such as marijuana to treat pain and depression. On a CNN poll conducted by Harris Interactive at 3 separate occasions the vast majority of people agreed that marijuana should be kept illegal with 59%, 73% and 78% agreeing[14]. This shows that people do not want a drug problem, so shouldn't this be the case for all drugs and enhancers? As the use of nanotechnology in combination with illegal drugs could cause even more problems for the medical profession, replacing the problems it prevents.

Dependence

The development of nanotechnology is a monumental task that could provide the world with a cure to numerous conditions and diseases. But the over application of this technology could have a detrimental affect on the way our bodies work and how they will be able to cope if the technology were to become unavailable. If nanotechnology was introduced as a standard everyday application in the future like a vitamin supplement can be used, would human bodies rely solely on the technology to carry out the functions it was just suppose to improve? Human bodies could change and effectively mutate to adapt to not needing to carry out that function itself, having a machine do it instead. Would the very technology used to improve life have a reversing effect? With everyone having to depend on machines to run their bodies normally and not just when they become ill, this dependence could seriously damage the progress of humanity and could even as has been depicted in the movies bring about an extinction of human kind. As the long term effects and potential problems of introducing nanodevices into the body are not understood at all, for example the carbon nanotube is very much like an asbestos fibre and could have the same poisonous effect if it were to be released into the air[15]. With it being made of carbon, it would make it a lot harder to detect and to then treat.

Conclusion

The advancements that nanotechnology can provide in medicine and other fields will be a revelation, as the technology will be able to be adapted and used on the vast majority of diseases and conditions that occur on the planet along with increasing the quality of life that people experience. The use of the dendrimer in particular will be a massive part of the future of medicine, as its versatility will be used to deliver drugs, diagnose disease, highlight specific cells, target obesity and cancer as well as performing a multitude of potentially unthought-of solutions to other conditions in the future.

With 1st generation: passive nanostructures commercially available now and 2nd generation: active nanostructures currently in development in a lab setting. Future 3rd and 4th generation nanotechnologies could take the technology that couple of steps further. In a current state of computational experiment and modelling phases, this could see the introduction of three dimensional nanosystems in the 3rd generation and eventually a full heterogeneous molecular nanosystem with each molecule having a specific structure and job to do in the 4th[2].

Unfortunately this technology will not be available for quite some time, as the problem with nanotechnology is that not enough is known about its long term effects on the body and the potential ways that it could cause damage. With all potential ethical problems considered and regulations for these dilemmas having to be put in place by a governing body. Such as the Foresight Institute, before they can occur in application to patients or before they become part of society and made irreversible. This will guarantee that nanotechnology is safely used when administered to patients and that there are set procedures for anything that could occur from the use of nanotechnology.

These problems can be solved by extensive testing and research into the subject with the combined effort of leading countries in the field of nanotechnology. But the research will take time, and that is time that some people don't have, with a balance between safely implementing the technology to patients and reducing the research time so that it can be applied, having to be made.

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