NANOTECHNOLOGY “TO BE OR NOT TO BE” – INVESTIGATING THE MEDICAL DEVELOPMENTS IN NANOTECHNOLOGY AND THE PROMISING FUTURE FOR PATIENTS

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Abstract

Nanotechnology has developed significantly in recent years due to its novel and sophisticated ability to gain control over matter on nanoscale, producing unique materials with useful properties and behaviour. Nanotechnology developments propose prospective solutions to fatal diseases such as cancer and this is an area currently growing and receiving much attention from nanotechnologists as it provides widespread applications. This paper discuses both current and possible future developments in nanotechnology especially in early diagnosis and prevention, specificity of treatment and personalized therapy as well as looking at some of the difficulties encountered during recent research. This paper also briefly mentions the ethical issues and dangers of nanotechnology.

Introduction

The complexity of the human mind and the ability of human beings to look beyond the range of human senses, which helps to catalyse novel technological breakthroughs, is not a new concept. Therefore, the rapid advancements in nanotechnology research are not surprising despite having only recently been an unknown concept, yet it is already said to be the next industrial revolution. Nanotechnology has become a worldwide phenomenon, where the leading scientists are involved in developing the new ideas into reality and incorporating them into everyday lives. Interestingly, in Russia a new project has been launched this year under the name “Russia-2045” in which nanotechnology can create an artificial human body which should prolong the human life. The scientists claim that they will be able to recreate interfaces, organs and systems that resemble the human being in every way by 2045 [14].

The importance the government has placed on nanotechnology should be mentioned. The funding from the government and industry was calculated to be astonishingly around US $10 billion globally for 2005 (Lux Research, 2006a) and by 2014 the cost of nanotechnology products will be over US $2.5 trillion (Lux Research, 2004) which again emphasises the infectious spread of enthusiasm over this revolutionary concept [9]. Yet, what is exactly nanotechnology and to what extent is the new phenomenon overestimated? Are we rightly spending such amounts on nanotechnology research or is it just another “much ado about nothing”? [9]

To fully comprehend this concept, one must gain an understanding of the basics of nanotechnology and its origin, placing great emphasis on the new promising medical developments.

Nanotechnology comes from the Greek word “nano” meaning “midget” and represents one billionth of a meter. Nanotechnology could then be defined in general terms as all man-made objects which have nanoscale dimensions, with specific useful properties that arise from their nanodimensions [13]. It is these unique and new properties that allow nanotechnology to be used in various developing fields of medicine to solve crucial long-standing world health problems.

But firstly, the development of nanotechnology must be studied to gain a greater awareness of the new inventions and improvements. Richard Feynman is said to be the first man who was aware of the promising concept of working in nanoscale and in 1959 put forward the idea that having the power to manipulate molecules and atoms would open countless opportunities for future developments [9]. In 1980s, Feynman's idea became a reality as individual atoms could now be manipulated, which then sparked off the discoveries of fullerenes, carbon nano-tubes and quantum dots, which are the basic roots from which further discoveries are now being made and which simultaneously succeeded in heightening the public's awareness of the new phenomenal concept and its future discoveries and benefits [9; 16].

A few important inventions in nanotechnologies relating to medicine must be addressed. Firstly and most importantly, research is now being made in areas concerning the detection of diseases and early diagnostics which can be made by the introduction of nanoparticles intravascularly into the patient which perform a specific diagnostic or therapeutic action at their directed site [15]. A specific type of brightly glowing nanoparticles called the "Cornell Dots" may soon be used to light up cancer cells which in turn will be able to help the diagnosis of cancer. Cornell dots are silica spheres to which organic molecules that are present in the tumour surfaces can attach, making the Cornell dots bind to the tumour cells. "When exposed to near-infrared light, the dots... serve as a beacon to identify target cells." [11] This novel development will be able to "show the extent of a tumour's blood vessels, cell death, treatment response and invasive or metastatic spread to lymph nodes and distant organs." [11] This consequently will enable a higher specificity in cancer treatment as it will heighten the understanding of the patient's condition so that the best method of treatment can be identified. Developing a personalised treatment is of great importance in modern society as with the current increasing demands for new developments, it is unacceptable to have a treatment that is effective for only 80% of the patients [15]. This leads onto the next development in the field of individualised therapy, where nanotechnology has already proved to have had a profound clinical effect on the drug-delivery systems. The specific scale of nanotechnology allows surface alterations of nanoparticulates in addition to having the ability to control the size and shape of the particles [15].

It could be seen that nanotechnology is accelerating upwards and may soon become the leading research of this century. However, as with all research there are a number of hurdles that must be conquered such as the biophysical barriers that must be overcome if the therapeutic agent is to be successful in reaching the affected or diseased cells. Other concerns, such as ethical issues associated with nanotechnology must also be considered when examining the advantages the future developments could bring.

Discussion

A great amount of research has been put into developing novel approaches to cancer therapy. This is rightly so, as cancer is a huge cause of mortality, with more than 10 million people affected every year [10]. In 2005, cancer became the leading cause of death of under 85 year olds in the US, leaving the cardiovascular disease trailing behind [20].

So what causes cancer and how can future developments in nanotechnology help?

Essentially, cancer arises on a nanometre scale and could simply be described as an error in the DNA. It starts as a localised disease but can soon spread rapidly, and this eventually makes cancer incurable. Up to date, the common treatments for cancer are invasive and crude: chemotherapy, radiation and surgery [16]. This often does not provide a sufficient enough treatment as there are a large number of life threatening side effects as a result of damage to healthy living cells, as well as tumour cells. This is because the current cytotoxic agents are not selective and cause damage to normal cells replicating in the bone marrow, gastrointestinal epithelia and hair follicles [20]. This non-specificity leads to an increase in the risk of endometrial cancer by 2.4 times and is a cause of major heart problems such as ventricular dysfunction and congestive heart failure [20]. Thus, it is of significant priority that novel approaches to selective delivery of cytotoxic agents to tumour cells are developed which will consequently improve the therapeutic index. Furthermore, treatments such as chemotherapy used for cancers that are increasingly proliferative and aggressive increases the risk of local and systematic recurrence [20].

Firstly, it is worth highlighting that developing the field of nanotechnology that deals with early detection of cancerous cells would be the most beneficial. Being able to identify cancer on a cellular level, before any apparent symptoms are present will not only prolong the life of the patient but will make it easier to treat as only a small number of cells, rather than a colony containing a billion cells will be present. Instead of looking for large tumour masses nanotechnology could inspect each cell of the patient and consequently remove the malicious disease. Rapid developments are already being made in this field. However, improvements could be made so that nanotechnology can be used to examine cells that are susceptible to cancer and determine what exactly causes it and most importantly be able to examine a healthy patient and determine the risk of cancer developing. For this, patients must have a routine check up, especially if the risk of developing cancer is high, so that it can be eliminated as early as possible.

Clearly, the above may present a serious challenge as clinical symptoms sometimes only become apparent when cancer has progressed into the fatal stage so another area of development should be considered. Developments in nanotechnology must be made so that the desired concentration of therapeutic agent can be delivered directly into the cancerous tumour cells and destroy them, without unwanted damage to normal cells. The fact that the nanoscale of nanoparticles allows a variety of properties to be exhibited, means that they can be specifically developed to carry a high concentration of drug, as well as a high quantity of the drug only to cancerous cells [10]. Targeted drug delivery will eventually eliminate surgery, radiotherapy and chemotherapy. A large number of developments in this field have been made already and it is worth mentioning a widely used chemotherapeutic agent doxorubicin which is used to treat breast, ovarian, bladder and lung cancer [1]. It is very effective as it blocks an important enzyme topoisomerase II and consequently prevents the DNA from replicating [1]. However, there are many side affects to doxorubicin such as permanent myocardial toxicity and lethal congestive heart failure. Evidently, this is an area for improvement. Current research suggests that these side effects can be partially eliminated by encapsulating doxorubicin in nanoparticles. In addition, it leads to an increase in the circulation time and consequently enhances the therapeutic efficiency when dealing with solid masses of tumour [1; 20]. However, the side effects are not eliminated but reduced, so that the patient still suffers mild side effects, thus, not improving the quality of life of the patient to a desired level. Moreover, there is a large variety of responses amongst patients to a specific treatment and, therefore, the side effects will vary, meaning that in some cases the reduction in side effects may be minimal. Furthermore, liposome based drug delivery systems that have been studied for a number of years are limited. These limitations include insufficient stability, low drug loading and complications in sterilisation [1]. Therefore, improvements are still required to be made in this field, so that a sufficient quantity of the drug can be safely delivered to the tumour without causing any side effects. Only then could the quality of life of patients suffering the disease be improved, as the fear of consequences and the ambiguity of the treatment would be reduced almost to nothing.

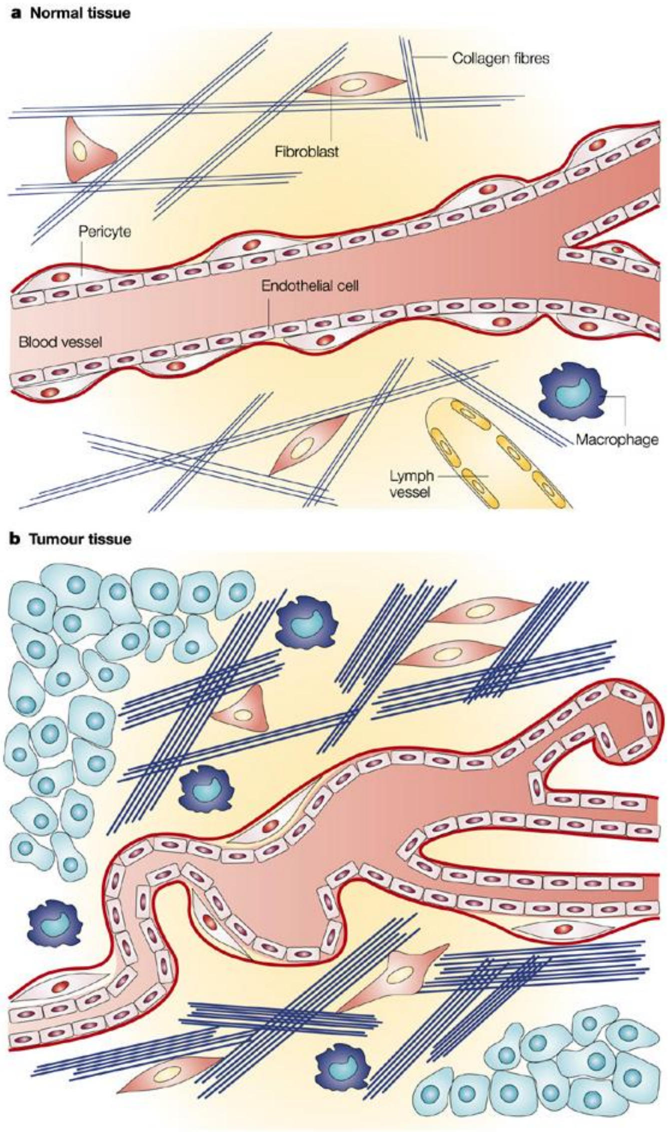
The next development I would like to mention is the need for the advances in personalised medicine, which will not only be able to overcome tumour heterogeneity but will also improve drug-delivery outcomes. Response rate for different marketed drugs alters with patients as demonstrated by figure 1.

Figure 1: Estimated response rate variability for marketed drugs [20]

Disease	Efficiency
Alzheimer’s Disease	70%
Cancer (brain, breast, lung)	70-100%
Depression	20-40%
Hepatitis C	53%
Hypertension	10-70%
Migraine	30-60%

Thus, from the above table, it should be noted that this issue does not only concern cancer but numerous other diseases. On top of that, it has been proved that 6.7% of patients admitted into the hospitals developed adverse drug reactions (ADR) during pharmacotherapy, with 0.32% lethal ADRs which lead to the deaths of around 100,000 patients per year in the U.S. [21]. This is where nanotechnology steps in and could be used to provide a balance between highest therapeutic efficiency and lower toxicity. Developments are being made where nanotechnology is being used for "targeted drug formulations that achieve maximum efficiency and optimal safety profiles" [21, 14]. This would consequently decrease the rate of fatal ADRs developing and increase patients' confidence that they are getting the best treatment possible, that is specific and that has been developed with the phenotypic variation in pharmacology in mind.

Figure 2



Another crucial issue is the obstacles of anti-cancer therapies which are presented when a cancer therapeutic agent tries to reach the tumour mass but has to overcome several physiological and biophysical barriers which limit its effect due to the loss of volume or activity in the blood circulation. One of the barriers that I would like to focus on is the increased interstitial fluid pressure (IFP) which is present in most solid tumours and which results in the decreased transcapillary transport and limits the time that the drug is maintained in the tumour [20]. Therefore, this is a major area for improvement as it causes the decrease in the uptake of therapeutic agent into the tumour. As can be noted from figure 2 [19] tumour contains a higher number of fibroblasts compared to normal tissue attached to the collagen fibres and which consequently causes a greater tension between the fibres in addition to the increase in the number of inflammatory cells [19]. These cells produce cytokines which exhibit an effect on blood vessel cells and stroma fibroblasts thus causing the increase in the IFP. Since the tumour interstitial fluid pressure is high, the drug is pushed back from the cancerous cells into the circulation and this prevents the drug from reaching the tumour [20]. This clearly leads to the decrease in the treatment efficiency, and the disease persists. It is also important to highlight that there is a direct relationship between the mean IFP and tumour size [20]. Therefore, this leads back to the lack of novel methods of prognosis. Combining the new nanotechnology developments in the field of identifying the cancerous cells at an early stage and being able to overcome the high IFP will enhance patient treatment. Looking even further into the future, nanotechnologists may be able to create multi-functional nanoparticles that will not only be able to identify the cancerous cells at an early stage of development but will also be able to treat or eliminate those cells at the same time, overcoming the biophysical barriers.

The injection of paclitaxel has proved to reduce the mean IFP by around 36% [20]. This is not, however, at a level that is desired and, therefore, I would like to suggest a number of other methods of dealing with the high IFP. Firstly, being able to lower the IFP before the drug is admitted will increase the interstitial transport of the therapeutic agent and access to the tumour cells can be gained. This is an area already being researched but without any major breakthroughs. Another approach to this may be to increase the pressure at which the drug is admitted, so that the pressure of the drug in the interstitial cells is greater than the tumour interstitial fluid pressure. For this, nanoparticles can be specifically modified so that their shape and size provide the greatest pressure, taking into consideration the progression and localisation of the disease, making the treatment patient specific by being able to take this into account and form a stable hypothesis concerning the level of the IFP that has to be overcome. Since pressure is given by force over area, by increasing the force (this could be done by increasing the mass of the nanoparticles) and decreasing the surface area will increase the pressure. Also, according to Boyle's Law pressure is inversely proportional to volume, and therefore, decreasing the volume will increase the pressure. Taking all of this information into consideration, nanoparticles can be developed that exhibit those properties and carry the therapeutic agent to the tumour cells, overcoming the barrier. In addition, limiting the oxygen available to the cancerous cells may cause some of the affected cells to die and therefore the IFP in this region will be lowered to enable the drug to exert its affect.

Having described the numerous potential future developments in nanotechnology relating to medicine and the benefit to the patient treatment and recovery, especially from cancer, it is highly beneficial to mention the ethical issues associated with nanotechnology. Not only the new opportunities must be examined, but also the risks presented both foreseen and unpredictable, where the benefits must clearly outweigh the risks. As discussed earlier, promising developments are already being made concerning therapeutic use of nanotechnology. Nanoparticles are specific and have the ability to kill only cancerous cells but this may present a number of risks about the interference with cell functions as a direct result of the novel properties that make them so efficient at delivering therapeutic agents to the affected cells [18].

Moreover, up to date the length of time that nanoparticles remain in the body is unknown and, consequently, this presents unforeseen risks to human health.

I would like to focus on an important danger presented which is the pulmonary toxicity of carbon nanotubes. Carbon nanotubes (CNTs) present various unique and novel physical and chemical properties and are extremely beneficial in biological and medical applications. However, they present a number of serious risks that must be carefully considered. CNTs can enter the lungs through inhalation and pass into the respiratory tract. This could happen as a result of exposure to CNTs as a result of biomedical use. Lung toxicity of CNTs is due to the properties CNT material exhibit, which includes “their structure, length and aspects ratio, surface are, degree of aggregation, extent of oxidation, bound functional group(s), method of manufacturing as well as to their concentration and dose” [6, 41]. Different *in vitro* studies have proved that CNTs can provoke oxidative stress, pulmonary fibrosis and prominent pulmonary inflammation upon reaching the respiratory tract. It was found that the toxicity was due to the metallic contamination of CNTs on the lungs. CNTs contain metal catalysts such as iron and nickel which add to the oxidative stress. The iron-containing raw nanotubes caused mild signs of inactivity, piloerection, hypothermia and shivering in mice. This suggests that iron catalyst add to the toxicity of CNTs and, thus, this is an issue that has to be dealt with in order to enhance the quality of the nanotechnological developments [6].

Overall, the significant developments in nanotechnology that have the potential to enrich people’s lives outweigh the ethical issues associated with using nanotechnology as a great amount of work has been put into raising awareness about nanotechnology and eliminating the predictable dangers and researching the potential unforeseen dangers in the future.

Conclusion

Nanotechnology is a major area for scientific breakthroughs that could enrich the lives of patients suffering fatal diseases such as cancer. Potential developments are already highlighting the benefits of nanotechnology research: the future promises to eliminate cancer as an incurable disease as it can be detected and treated at an early stage using methods that are non-invasive.

On the other hand, there are clearly many hurdles to be overcome for this to happen. There are still various barriers such as the high fluid interstitial pressure mentioned earlier and also a number of other equally challenging obstacles which hold back the developments such as the tumour vascular architecture, cellular uptake of therapeutic agent and tumour heterogeneity. Although I have mentioned a number of possible ways to reduce the high IFP, this may not necessarily provide a big enough difference. Thus, all the barriers must be overcome for the treatment to be effective on all the patients.

This leads on to the another difficulty: patient specificity. I have stressed this point earlier and would like to mention that although *in vivo* experiments on mice have proved to have a positive effect, this may not be the case for all patients and of course may have adverse effects on the human body compared to mice. Therefore, this will not be able to provide efficient enough specificity. A variety of different non-invasive methods must be created, so that there is a greater chance of successful treatment available for each patient.

Moreover, another issue which may arise in the near future must be mentioned. As the use of new nanotechnological methods at present are limited, they are used only on a small percentage of the patient population. This limitation may provide a class segregation regarding treatment. More pressure will not only be put on the patients but also on the doctors who will have to make crucial decisions about the patients that require the novel methods the most. In addition, some patients may be able to afford the treatment whilst others, although in greater danger, may not have such an opportunity.

The decision must also be made regarding the amount of research and developments that must be put into developing new approaches to dealing with various diseases. Whilst cancer is a major cause of mortality where numerous useful developments have already overridden the old therapeutic drugs, HIV, for example, which at present cannot be cured, is given far less attention. This to some extent highlights the unreasonable approach to medical developments in nanotechnology.

Conclusively, nanotechnology provides a bright future as a novel and unique generation of cancer detection and treatment. It is developing with lightening speed to turn the theories into reality and incorporate the new technological advances into every-day medicine. However, there are still various issues yet to address.

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