

NANOTECHNOLOGY IN THE DIAGNOSIS AND  
TREATMENT OF LIVER CANCER

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**PASS WITH MERIT**

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## Abstract

Nanotechnology is a branch of engineering that deals with structures smaller than 100 nanometres, and the manipulation of these models at both atomic and molecular level. Nanotechnology offers considerable potential in developing a wide range of applications which can lead to numerous socio-economic benefits. This paper will primarily focus on the prospect of implanting nanoscale devices – such as nanotubes and nanoscaffolds – into the body for the diagnosis and treatment of liver cancers. As the UK's drinking culture becomes ever more ubiquitous, liver cancer is a significant issue today. Therefore, it is imperative to explore the future medical applications of this field and the ethical issues which surround them.

## Introduction

### *Principles of Nanotechnology*

Nanotechnology is defined as the engineering of functional systems at the atomic and molecular scale. In its original sense, nanotechnology refers to the projected ability to build up structures molecule by molecule using numerous techniques and tools.

In order to understand how this tiny world of nanodevices works, we need to get an idea of the units of measure involved. A micrometer is one-millionth of a meter, but this is still relatively large compared to the nanoscale. A nanometre is one-billionth of a meter – smaller, even, than the wavelength of visible light. Fundamentally, nanotechnology seeks to imitate nature, in building from the bottom upwards.

“Nanomedicine” is the term that has been employed for applications of nanotechnology relevant to medicine. This relatively new science could provide us with endless possibilities – perhaps in the near future we may even be able to grow complex organs through this technology.

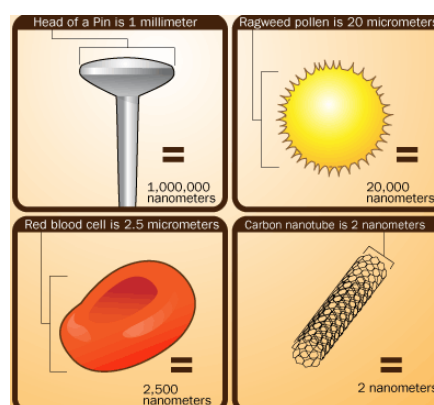


Figure 1

### *History of Nanotechnology*

The first ideas of nanotechnological concepts arose from Richard Feynman's infamous speech “There's plenty of room at the bottom”. Here, he considered a number of interesting implications of an ability to manipulate matter at an atomic scale – Feynman proposed shrinking computing devices toward their physical limits.

The term ‘nanotechnology’ was only later created by Professor Norio Taniguchi, in a research paper in 1974, where he proposed: "Nanotechnology mainly consists of the processing of separation, consolidation, and deformation of materials by one atom or one molecule."

In 1986, Eric Drexler's ideas of nanotechnology, published in his book, “Engines of Creation: The Coming Era of Nanotechnology” led to the widespread acknowledgement of this term, whilst he also became the first to be awarded with a Nobel Prize in nanotechnology.

The discovery of  $C_{60}$ , Buckminster Fullerene (Figure 2) by chemists Richard Smalley and Robert Curl in 1985, was the next significant progression in the development of nanotechnology. 'Bucky Balls' are spherical structures, composed of a combination of pentagons and hexagons. They are the only molecules composed of a single element to form a hollow spheroid. This internal cavity, combined with its resistance to collision, provides the potential for novel drug-delivery systems.

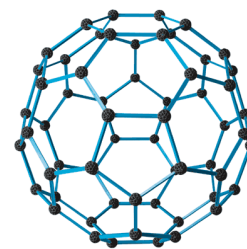


Figure 2

### *Current Applications of Nanotechnology in Medicine*

Owing to the vast possibilities nanotechnology has to offer, it is currently being used and developed across a range of fields – the following includes examples of its application in medicine today.

Sunscreens are utilizing nanoparticles that are particularly effective at absorbing ultra-violet light. Due to the minute particle size, they spread more easily and have better coverage. They are also transparent, unlike conventional screens which are white – encouraging their use as a means of protection against skin cancer.

Furthermore, nanocrystalline silver particles are in use as an antimicrobial agent on dressings for wounds. These particles, with an incredibly large surface area, inhibit bacteria using two methods: disrupting cellular respiration, or by damaging the bacterial cell wall. As antibiotic resistant bugs such as MRSA are becoming increasingly difficult to treat, silver-coated dressings help to contain the infection and prevent their spread. In this way ill patients, who are already subject to reduced immunity, are less likely to be infected by hospital superbugs.

## Discussion

Liver cancer incidences are on the rise; increasing by more than one third in the past 20 years. Many believe this is due to lifestyle changes in the UK, with ever increasing alcohol consumption correlating with this rise in liver cancer cases. Thus, liver cancer has become a prevalent issue today, necessitating further research into the fields of diagnosis and treatment of cancer.

Figure 1.3: Age standardised (European) incidence rates, liver cancer, by sex, UK, 1993-2007

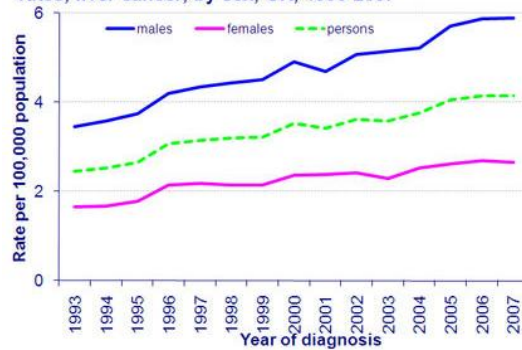


Figure 3

## *What is Liver Cancer?*

Liver cancer is one of the most common cancers in the UK with 3,407 people diagnosed in 2007. As with the majority of cancers, age increases the likelihood of obtaining the disease, with 7 in 10 cases occurring in persons over 65 years old.

In terms of primary liver cancers, two main categories exist; hepatocellular carcinomas (HCC) (Figure 4), arising from liver cells, and Intrahepatic cholangiocarcinoma, arising from bile duct cells. HCC contributes to 85% of liver cancers. It sometimes starts out as a single tumour and then grows larger, and only late in the disease does it spread to other parts of the liver. Alternatively, it tends to occur in people who have a damaged liver from cirrhosis. The outcome is generally poor, with only 10 - 20% of HCC patients amenable to a potentially curative surgical treatment. If the cancer cannot be completely removed, the remaining life span of the patient is dramatically reduced.

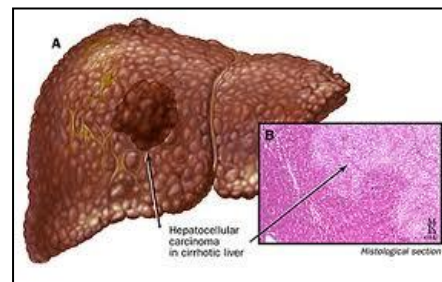


Figure 4

## *Who is at risk?*

Cirrhosis is defined as the consequence of chronic liver disease, characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated), leading to loss of liver function.



Figure 5

The damage could result from a number of risk factors, including hepatitis B and C, Aflatoxin and Type 2 diabetes. Alcoholism also poses a huge problem, with about one third of HCC cases due to excessive alcohol intake. Chronic alcohol use for more than ten years increases risk of HCC five-fold.

### *Current Methods of Diagnosis*

Liver cancer is particularly difficult to diagnose as in its earliest stages it is asymptomatic, and due to its position within the body, it is also hard for a doctor to feel. It is important to note that the diagnostic measures below are only catered to those with risk factors, such as those suffering from cirrhosis.

Method	Explanation
Contrast CT Scan	A type of X-ray which relies on administration of amplification agents such as chemical dyes.
Angiography	Dye is injected by a catheter through the main vessel that delivers blood to the liver – this allows the blood vessel to be viewed on an x-ray
Contrast MRI Scan	MRI uses radio waves and a powerful magnet to create images of internal organs and tissue.
Needle Biopsy	A small section of liver is extracted using a needle to be examined under a microscope.

### *Current Treatment of Liver Cancer*

Surgery, ablation and chemotherapy are the main treatments for liver cancer. Radiotherapy is not often used to treat primary liver cancer because the liver is not able to tolerate very high doses of radiotherapy.

#### *Surgery*

There are 2 main surgical procedures for the treatment of liver cancer:

Liver Resection: This type of surgery is generally only performed if only a small section of the liver is damaged, in which no major blood vessels are involved. This technique is a relatively simple one in which tumour cells, along with a small portion of surrounding healthy cells, are completely removed.

Transplantation: Liver transplants are mainly performed when the tumour is so advanced that resection is not possible, or where the liver has been damaged by further underlying conditions, such as cirrhosis. This type of surgery is generally less common than resection, as the donor liver must be a close match to yours, meaning there is often a long waiting list for transplants.

### *Ablative Therapy*

Ablation, is the local destruction of a tumour, and can be performed using several different types of energy.

Cryosurgery: (Figure 6) This technique uses liquid nitrogen, which is injected into select areas of the liver and destroys tumours by freezing cells. This procedure is unique, in that it has the ability to destroy large tumours that would otherwise be inoperable; however it also poses a higher possibility of damaging the surrounding healthy tissues and blood vessels.

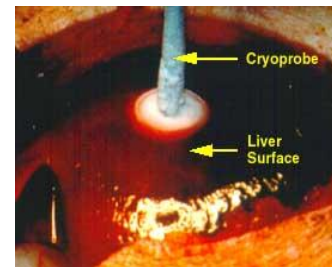


Figure 6

Chemical Ablation: This is a newer form of treatment, used to kill the tumour by chemical action (e.g. ethanol) however it is very painful.

With all of the types of treatment mentioned above, there is always a risk that the cancer may come back, as there is currently no way of detecting if the cancer cells could have broken off before the procedures took place

### *Chemotherapy*

Systemic (general): Chemotherapy uses cytotoxic drugs to destroy cancer cells. As they circulate in the blood, these anti-cancer drugs disrupt the growth of any cancer cells wherever they are in the body. Generally, chemotherapy is not a particularly effective treatment for primary liver cancer and can often result in side effects including nausea, peripheral neuropathy and anaemia.

Chemoembolisation (local): Most systemic chemotherapeutic agents are processed by normal liver cells. In patients whose liver function is impaired, however, the chemotherapeutic agent cannot be broken down and its toxicity can potentially be harmful to the patient.

Alternatively, chemoembolisation is often used as a treatment for liver cancer. It is a combination of the local delivery of chemotherapy and a procedure called embolisation. This avoids chemotherapeutic drugs affecting other organs and therefore bears fewer side effects.

## *Future applications of nanotechnology*

### *1. Nanotechnology in Cancer Imaging*

With any type of cancer, early detection is extremely important. In its earliest stages, a tumour is small and localised; therefore the cancer can be treated with a curative intent. Over time, when a cancer spreads to other organs, however, the patient can only receive palliative care. In terms of liver cancer – particularly for those who suffer from cirrhosis – early detection of primary liver cancer greatly improves the chances of survival after treatment. This is why regular liver cancer screening is so vital in patients with risk factors.

Current methods of imaging only detect cancers after they have made a visible change to a tissue. By this time, thousands of cancerous cells will have multiplied, if not metastasised. Once detected, further time is taken whilst the treatment is assessed and biopsies are taken. Nanotechnology opens the door to the possibility of cancerous, pre-cancerous or even unstable liver cells (which often progress to becoming cancerous) being tagged, allowing detection of these cancers far sooner. This is achieved as nanoparticles can both specifically identify cancerous cells and enable them to be seen.

Antibodies that identify specific receptors abundant in cancerous cells can be coated onto nanoparticles, such as metal oxides, which produce a high contrast on MRI or CT scans. Alternatively, quantum dots (Figure 7) could be attached to the nanodevice. These dots are nanoparticles that emit photons when stimulated by UV light. The wavelength of these photon emissions depends solely on the size of the dot,



Figure 7

thus an infinite number of different colours can be produced. This diversity allows scientists to create quantum dots which will be able to detect and/or bind with many different types of cell or DNA mutations that cause cancer. Once inside the body, these nanoparticles will selectively attach to the cancerous cells, thereby illuminating their location on the scan. This would allow doctors to see molecular markers that pin point specific stages of cancer far earlier than current imaging techniques.

Moreover, if unstable liver cells could be destroyed even before becoming pre-cancerous, cancer could be avoided altogether. Unstable liver cells is highly likely to develop to a pre-cancerous stage, thus, in binding with the cells, this alerts doctors of these risk areas and enables them to be destroyed.

The overall advantage of this method is that quantum dots have the ability to detect even the smallest of tumours. Early detection will always allow for a better prognosis, as the later the diagnosis, the more likely it is to have spread. This method could also eliminate the need for radioactive markers, which pose a difficulty, as they often have short half lives.

## 2. Nanotubes

Nanotubes are molecular-scale tubes of graphitic carbon with many useful properties. They are among the stiffest and strongest fibres known, and have remarkable electronic properties and many other unique characteristics.

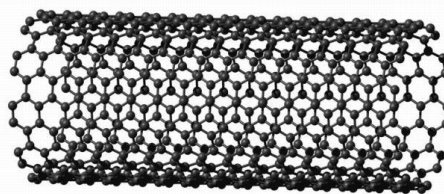


Figure 8

The current interest in carbon nanotubes is a direct consequence of the synthesis of buckminsterfullerene,  $C_{60}$  in 1985 – the discovery that carbon could form a stable, ordered structure other than graphite and diamond. The nanotubes build on this technology, containing at least two layers, and range in outer diameter from about 3–30 nm. They are invariably closed at both ends although nanotubes are still able to take various shapes.

Recently, nanotubes have been developed to improve drug delivery, particularly to patients who suffer from cancer. Since nanotubes are hollow, this allows a drug to be stored within them and once in the body they could be activated to release the drug. This method is only likely to succeed if the nanotube could be made to be highly inert, so as not to react with the chemotherapy contained within it. There is also the problem of tracking the nanotubes once inside the body, to ensure they release the drugs in exactly the right place. One way of ensuring this is to attach antibodies specifically capable of binding to cancerous cells to the outside of the nanotubes. Additionally, quantum dots – highly luminescent particles – would enable easy tracking of the nanotubes. These quantum dots are able to fluoresce almost indefinitely, thus it is possible to leave the nanotubes in the body for some time, so the chemotherapy can be released at regular intervals using an incredibly non-invasive method.

As the sheer scale of nanodevices allows us to pin-point their precise location – chemotherapy can be delivered even more specifically to solely the cancerous cells – minimising the risk to other fast growing, yet healthy cells such as hair and nails. A further advantage, therefore, is that much of the social and psychological effects of current cancer treatment will be minimised.

One drawback is the question of whether or not nanodevices can exist in the body on a long term basis without a problem, such as rejection as nanodevices are, fundamentally, foreign bodies. However, it is possible that this could be solved if the devices were primarily composed of carbon – just like the body – meaning rejection could be reduced. It should also be noted that pacemakers have also overcome this problem.

### 3. *Nanoscaffolds*

Nanoscaffolding (Figure 9) is the medical process utilized for the regrowth of tissue and bone, using a microscopic apparatus made of fine polymer fibres called a scaffold. The scaffold acts as a trellis for the damaged cells, which bind to the structure, with the incredible ability to arrange themselves into the correct order when given a suitable foundation to develop around. The fibrous structure of nanoscaffolds has been designed to mimic the natural collagen fibres found in the body, thus they are extremely porous, with tiny holes for cell attachment and protein adsorption. These features encourage both cell differentiation and tissue development.

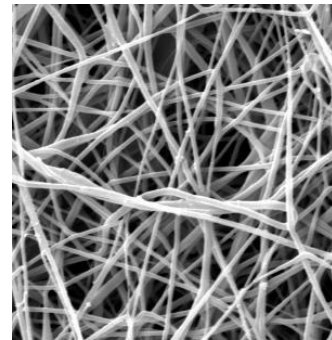


Figure 9

The technique, which was developed by Military researchers in 2006, has already been used in several situations. For example, nanoscaffolds have been used to regrow the skin of third-degree burn victims, and the optic nerve of several mice in a laboratory experiment.

It is proposed that nanoscaffolds may possess the potential to allow complex organs to be completely regrown using this method of assembly. Currently, the main factor which prevents this prospect is the inability to produce the supporting vascular systems which are necessary for our internal organs. However, researchers from Massachusetts Institute of Technology have recently been able to produce a miniature functioning vascular system: "We used living vessels as a guide to model factors such as the angle and size ratio between branching vessels. But we optimised our design to improve it," said lead researcher Mohammad Kaazempur-Mofrad. The system in question, despite only being able to function correctly inside a small mammal, such as a rat, provides scope for creating a similar structure within humans. The combination of this technology and that of nanoscaffolding theoretically provides the basis for a fully functioning organ.

Current surgical treatments for liver cancer either involve the removal of a section of the liver, provided the tumour in question is relatively small, or transplanting the entire organ for a new, healthy one.

The primary drawback of the first method is that often the tumour is so large, there is simply not enough healthy organ left to function inside the body. However, the insertion of nanoscaffolds to encourage tissue development could lead to the regrowth of an entirely healthy liver. This organ already possesses extraordinary regenerative powers, in its ability to regrow following up to 70% of its mass being removed through surgery. These abilities make it one of the most likely organs to succeed in being fully regenerated through the technology of nanoscaffolds.

Transplantation also proves an issue, in that donors must be a close-match for the destroyed liver, often leading to huge waiting lists for very few healthy organs. Nanoscaffolds provide scope for creating several organs from healthy ones, thus reducing waiting lists, and preventing secondary tumours from having time to form.

## *Ethics of Nanotechnology*

### *Bioterrorism and Grey Goo*

From various investigations into nanotechnology, several long-term major risks to society and the environment have been identified. For example, the possibility of bioterrorism – of having terrorists with more powerful, stronger and much more compact devices – poses a major risk to society. Through the science of nanotechnology, biological weapons would become far easier to conceal, and defences against these devices may not be immediately installed.

The idea of ‘grey goo’ has also been a topic of discussion in relation to the ethics of nanotechnology. The term refers to a hypothetical end-of-world situation, in which the world is consumed by self-replicating nanobots, and was initially used by Eric Drexler in 1986. The possibility of this situation has led scientists to pose the question of whether it is worth risking the fate of our planet for the benefits that nanotechnology can have on the way we live our lives.

In Britain, Prince Charles called upon the Royal Society to investigate the "enormous environmental and social risks of nanotechnology - The Royal Society's report on nanoscience was released on 29 July 2004, and dismisses the idea of “grey goo” as impossible. Furthermore, recent investigations have further invalidated the grey goo hypothesis as an accidental situation; however the possibility of grey goo being developed on purpose is still a source of discussion and concern.

### *Funding*

The budget for nanotechnology is ever increasing. (Figure 10) With so many resources dedicated to its development, nanotechnology will surely have an impact within our lifetime, so it is important to examine its ethical implications while it is still in its infancy. One of the largest implications of nanotechnology

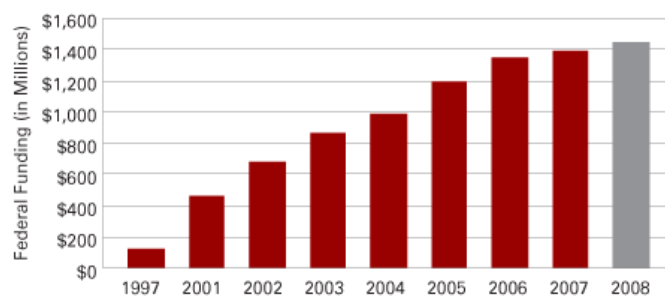


Figure 10

would be the sheer expenditure on research, and the cost of its treatments for patients in the future. At the moment, nanotechnology is the most expensive of all technologies, therefore we must ask ourselves: is it worth it? With many developing medical trials still waiting to be approved it seems that the disadvantages of nanotechnology could outweigh the benefits.

Even if these costs could be covered, there is still the risk that the transplanted part of liver may be rejected by the body's immune system due to the white blood cells recognising it as a foreign body and destroying it. Secondly, with today's drinking culture as it stands, people are inflicting these problems upon themselves by choice. So why is so much money being pumped into this branch of nanotechnology technique? Is it really worth the NHS's precious time? The fact is that this process is extremely expensive and with the rate of rejection of a transplanted liver at 10% and

cultural norms as they are, there is a significant chance that after all this expenditure, it could be viewed as a waste of time and money.

However, for the other 80-90% of patients who own a functioning transplanted liver after a year, it makes a huge difference to their lives, as without this newly developed technique they would not have survived. In regards to the problems that arise due to alcoholic consumption, there is an intense screening process of those who are and are not deserving of transplants already in place and it is, therefore, worth funding in the long-run. From this perspective it is difficult for anyone to deny that nanotechnology is not worth the time and money

### *Religious Point of View*

There is a direct correlation between people who bear religious views and the disapproval of nanotechnology in medicine. The primary conviction against it is that it is a means to unnaturally enhance human qualities and is, fundamentally, “playing God”. It has been found that countries where religious belief is strong, such as Ireland and the US, tended to be the least accepting of nanotechnology, whereas those where religion is less significant were more accepting of this technology. The rejection of this technology by religious countries is based on the technology’s potential to create life at a nanoscale.

## Conclusion

This paper has primarily focused on the diagnosis and treatment of liver cancer, due to its huge projected rise in the coming years. Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths in 2008 – 700,000 of which were due to liver cancer – and is predicted to increase to over 11 million by 2030.<sup>1</sup> For this reason, further action is evidently needed, and this paper proposes nanotechnology as a way forward.

It is important to note that although the developments proposed in this paper have a solid foundation in the properties of nanotechnology, this experiment is theoretical as it is a Gedanken – where there are limited time and resources available. The ideas put forward have built on those already undergoing primary research; this paper has expanded upon those which already exist.

Ethically speaking, nanotechnology is considered an extremely controversial topic. Many people hold religious views that conflict with the ideas that nanotechnology strives to develop; it is believed to be unnatural and “playing God”. In terms of bioterrorism, the outcome of “grey goo” is virtually impossible to result from the uses of *nanomedicine* proposed in this paper. On balance, with regard to the topics discussed in this paper, these numerous objections should not play such a significant role.

Nanoscaffolding provides a way forward in the potential regrowth of liver tissue. This pioneering research could have several benefits for the NHS, such as reduced waiting time for organs. Meanwhile, early detection of liver cancer allows the cancer to be diagnosed and treated before resorting to transplantation, whilst increasing chances of survival after treatment. Furthermore, this eliminates the need for long-term palliative care which can be both time consuming and emotionally straining. A further alternative sub-field of research is the development of nanotubes to deliver chemotherapy specifically to the cancerous cells.

Although several developments have been proposed; prevention is always better than cure. The prospective ability of nanotubes to detect unstable cells in the formation of scar tissue in liver cirrhosis, even before they become pre-cancerous, is an invaluable tool. By preventing even the onset of cancer, the NHS can save both time and money that would otherwise be invested into treatment plans. Particularly given the current financial climate, it is imperative that we do all we can to save these vital resources, and we propose nanotechnology is the most effective way of doing so.

## References

[www.who.int](http://www.who.int)  
<http://www.newscientist.com/article/dn3916-nanotechnology-may-create-new-organs.html>  
<http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/liver/hcc.pdf>  
<http://www.scu.edu/ethics/publications/submitted/chen/nanotechnology.html>  
<http://science.howstuffworks.com/nanotechnology5.htm>  
<http://www.azonano.com/Details.asp?ArticleID=1977#> Cancer and Drug Delivery  
<http://www.nanowerk.com/spotlight/spotid=1781.php>  
<http://www.foresight.org/Nanomedicine/NanoMedFAQ.html>  
<http://www.foresight.org/Nanomedicine/NanoMedFAQ.html>  
<http://www.understandingnano.com/medicine.html>  
<http://en.wikipedia.org/wiki/Nanomedicine>  
<http://www.zyvex.com/nanotech/feynman.html>  
[http://www.worldlingo.com/ma/enwiki/en/Norio\\_Taniguchi](http://www.worldlingo.com/ma/enwiki/en/Norio_Taniguchi)  
<http://e-drexler.com/p/idx04/00/0404drexlerBioCV.html>  
<http://www.nanotech-now.com/nanotube-buckyball-sites.htm>  
<http://www.nanocotechnologies.com/content/AboutUs/AboutQuantumDots.aspx>  
<http://www.cancerbackup.org.uk/Treatments/Chemotherapy/Individualdrugs/Liposomaldoxorubicin>  
<http://www.cancerbackup.org.uk/Treatments/Chemotherapy/Individualdrugs/Cyclophosphamide>  
<http://en.wikipedia.org/wiki/Prodrug>  
<http://en.wikipedia.org/wiki/Cyclophosphamide>  
<http://en.wikipedia.org/wiki/Nanoshell>  
<http://www.hi.is/~thorstlo/prodrugs.pdf>  
[http://en.wikipedia.org/wiki/Quantum\\_dots](http://en.wikipedia.org/wiki/Quantum_dots)  
<http://www.bsg.org.uk/clinical-guidelines/liver/guidelines-for-the-diagnosis-and-treatment-of-hepatocellular-carcinoma-hcc-in-adults.html>  
<http://nano.cancer.gov/>  
[http://www.medicinenet.com/liver\\_cancer/page2.htm](http://www.medicinenet.com/liver_cancer/page2.htm)  
<http://www.physorg.com/news/2011-02-nanotechnology-treatment-liver-cancer.html>  
<http://www.nanotechnologist.com/new-organs/index.html>  
<http://www.shvoong.com/medicine-and-health/1702755-nanotechnology-create-new-organs/>  
<http://www.sciencedaily.com/releases/2007/05/070503205701.html>  
<http://www.nanotechnologist.com/>  
<http://www.nhs.uk/Conditions/Lung-transplant/Pages/Preparation.aspx>  
<http://www.tahan.com/charlie/nanosociety/course201/nanos/NH.pdf>  
<http://www.cancerhelp.org.uk/type/lung-cancer/treatment/surgery/types-of-surgery-for-lung-cancer#types>  
<http://www.tahan.com/charlie/nanosociety/course201/nanos/NH.pdf>  
<http://www.terasemjournals.org/gn0302/jp2.html>  
<http://www.cancerhelp.org.uk/type/lung-cancer/treatment/surgery/types-of-surgery-for-lung-cancer#types>  
<http://www.understandingnano.com/medicine.html>  
<http://www.nanohealthalliance.org/>  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676636/>  
<http://www.nanomedicinecenter.com/article/current-uses-of-nanomedicine/>  
<http://nano.cancer.gov/learn/impact/diagnosis.asp>