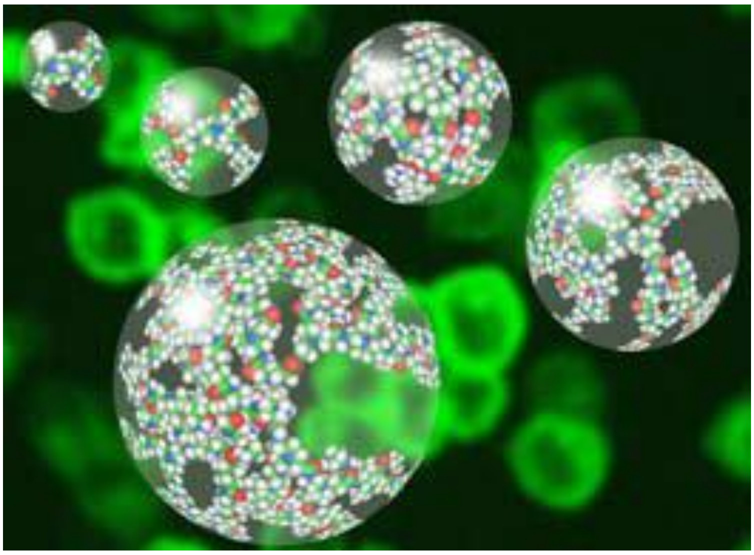
AN EXPLORATION INTO THE FUTURE DEVELOPMENT OF NANOTECHNOLOGY IN THE DIAGNOSIS, TREATMENT AND PREVENTION OF INFLAMMATORY BREAST CANCER



BY

RACHEL GEORGE

PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2010

Word Count: 3769

ABSTRACT

Nanotechnology is a mushrooming, multidisciplinary scientific field and is now at the forefront of medical research. This paper gives a short description of the current and possible future research on the use of nanotechnology in the diagnosis, treatment and prevention of the very aggressive inflammatory breast cancer. It explores the development and use of nanodevices that will seek out diseased cells in breast tissue, enter them, enhancing their visibility and either repair them or induce them to die. Nanooncology has a promising future and further advances will facilitate a personalised medicine approach to inflammatory breast cancer.

INTRODUCTION

Nanotechnology (derived from the Greek word *nano* meaning *dwarf*) is defined as the science and engineering involved in the design, synthesis and application of materials on the nanometre scale or one billionth (10^{-9}) of a metre. Nanotechnology has found numerous applications in medicine because the medical field deals with things on the smallest of levels. One of the greatest advances in nanotechnology is the development of new and effective medical diagnostics and treatments (i.e. nanomedicine).

Nanoscale devices are 100-10,000 times smaller than human cells (Figure 1). As a result, they can readily interact with biomolecules on the inside and surface of cells. They therefore have the potential to detect disease and deliver treatment because of their ability to infiltrate various parts of the human anatomy.

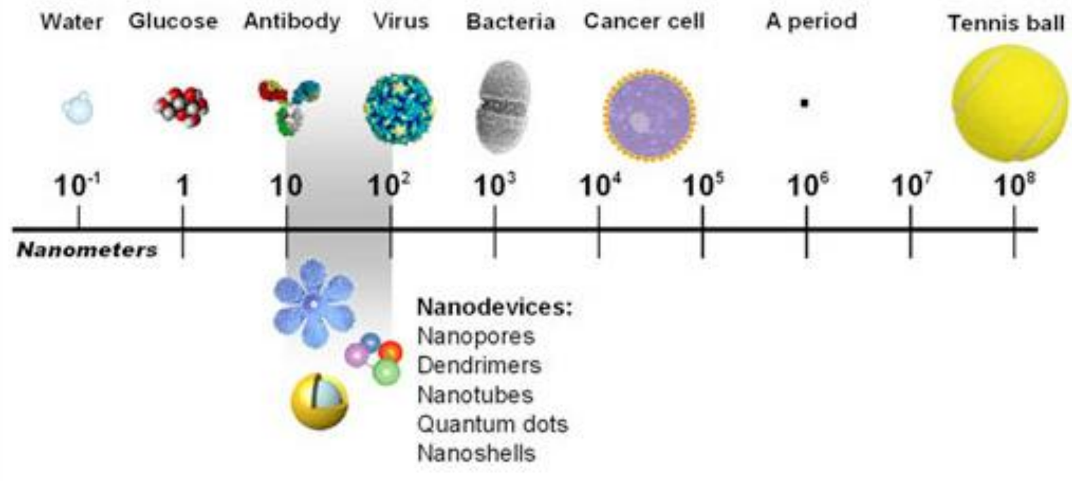


Figure 1

The National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer, is promoting nanotechnology in order to transform the diagnosis, prevention and treatment of cancer. The conventional methods for treating cancer include surgery, chemotherapy, radiation and many others. These methods are valuable if the cancer is detected soon enough. However, they are not effective enough because they do not only target cancerous cells, but also affect healthy neighbouring cells. It is crucial to accurately diagnose and treat cancer early on in its evolution from a microscopic disease to a metastatic disease. Nanotechnology has found many new ways in detecting cancer cells and how far the disease has spread throughout the body. The survival of cancer patients can be greatly improved with technological advances in the following areas; tumour imaging and early detection, procedures for accurate and early diagnosis and prognosis, overcoming the adverse side effects of chemotherapy drugs, by targeting and treating aggressive and lethal cancer phenotypes such as bone metastasis. This revolutionary approach is so precise that cancer detection, diagnosis, and treatment can be tailored to each individual's tumour molecular profile leading to personalised oncology. It will also lead to predictive oncology in which genetic and molecular markers are used to predict disease development, progression, and clinical outcomes.

Amongst the vast array of nanomaterials available, some of the most widely used forms include quantum dots, nanoshells, carbon nanotubes, and dendrimers, which are discussed below. Nanoparticles with metal elements usually have optical and magnetic properties that can be used for imaging. Therapeutic agents can be conjugated or encapsulated to nanoparticles. In this way chemotherapeutic drugs have been smuggled into cancerous cells and have delayed the growth of tumours.

Quantum dots range from 2 to 10 nm in diameter and are made of cadmium selenide semiconductors, capped with zinc sulphide. These nanocrystals possess unique optical and electronic properties. They fluoresce in different colours depending on their size after excitation with UV light. Larger particles emit light in the red end of the visible spectrum, whereas smaller particles emit in the blue range.

Advantages of using quantum dots over radioactive tags or organic fluorophores, such as fluorescein or cyanine dyes for *in vivo* applications, is that quantum dots have extended blood circulation time and can fluoresce for several months *in vivo*.
Quantum dots are therefore a topic of immense priority and are invaluable in cellular imaging and molecular profiling of pathological tissue specimen of cancer patients; this is the way forward for the diagnosis of stages of cancer, prognosis and directing the treatment strategy. At present, due to the toxicity concerns of the heavy metal, cadmium, the application of quantum dots is restricted to *in vitro* and animal studies.

Nanoshells are nanoparticles consisting of a silica core, coated with a thin gold shell. Nanoshells are injected into the bloodstream and as they circulate through the blood, they preferentially accumulate on cancerous cells. This occurs because tumours create numerous blood vessels very rapidly to feed their growth. These blood vessels have lots of defects and particles as small as nanoshells slip through the defects in the blood vessels and get localised naturally in the tumour. In the course of several hours, the nanoshells concentrate at the tumour site from the bloodstream. Scientists can also further embellish nanoshells to carry molecular conjugates to the antigens that are expressed on the cancer cells themselves. This type of specificity enables nanoshells to preferentially link to the tumour and not to healthy neighbouring cells. An external source of energy is then supplied to these cells. Nanoshells with a silica core diameter of ~120 nm and a 10 nm layer of gold shell are highly useful because they absorb this energy, creating intense heat that is lethal to the tumour cells. The result is highly selective with rapid tumour destruction and the surrounding tissue is left unscathed with no systemic toxicity (Figure 2).

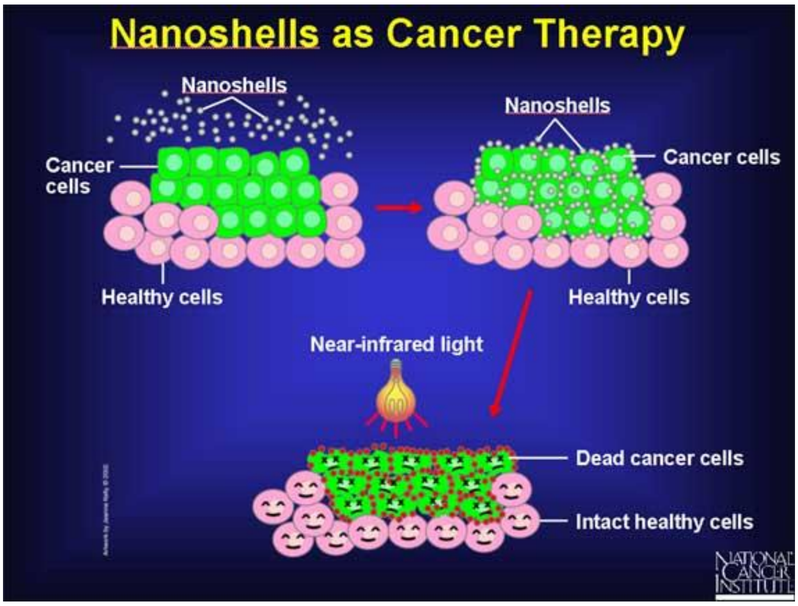
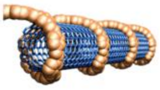


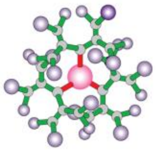
Figure 2:

The ability of nanoshells to scatter light is being utilised for cancer imaging; however, their primary use continues to be in thermal ablation therapy. Although, focused lasers for thermotherapy were useful, simple heating cannot discriminate between tumours and healthy tissue. With nanoshells, the energy can pass through the healthy tissue without causing harm, killing only the targeted tumour cells.



Nanotube

The **carbon nanotubes** discovered in the late 1980s are cylindrical hollow tubes consisting entirely of the element carbon and are 100 times stronger than steel with only one-sixth of its weight. They have been used to transport DNA molecules into the cell and also for thermotherapy. Folic acid has been adsorbed onto the nanotubes to allow specific binding to cancer cells. Upon irradiation with NIR, only tumour cells were selectively destroyed leaving normal cells, with a low level of the receptor, unharmed. The *in vivo* location of the nanotubes was viewed by attached fluorescent tags.



Dendrimers are repeatedly branched polymers that are 2-10 nm in diameter and spherical in shape. A water soluble dendrimer has a hydrophilic end-group. Water-soluble dendrimers with internal hydrophobicity have been designed, allowing it to carry a hydrophobic drug in its interior. The most commonly studied system has been the family of PAMAM (polyamidoamine) dendrimers, but the variety of building blocks is growing rapidly. The polymer branches provide a large surface area to which therapeutic agents and targeting molecules can be attached. Methotrexate-carrying dendrimers that could identify cells expressing folate receptors were also used to demonstrate successful *in vivo*-targeted drug delivery to cancer cells. These dendrimers also carried fluorescein as a tracking agent in addition to the drug and the biomarker.

Nanoparticles are able to combine and deliver many different functionalities simultaneously and specifically to a tumour due to their large surface area, diverse surface chemistry and unique pharmacokinetics. Most of the conventional anticancer agents do not differentiate between cancerous and normal cells and this leads to systemic toxicity and adverse side effects. Nanoparticles have been engineered to fix themselves onto tumour cells after systemic delivery. This is achieved by conjugating nanoparticles with a molecule or biomarker that binds to receptors found on tumour cells.

DISCUSSION

Cancer (also referred to as malignant tumours or neoplasms) is a generic term for a group of diseases that can affect any part of the body. A typical feature that defines cancer is the rapid multiplication of cells that can then invade neighbouring parts of the body and spread to other organs. This process is referred to as metastasis. Metastases are the major cause of death from cancer.

Cancer is a major public health concern in Britain. Every year more than 250,000 people develop the disease and half of them may die. Breast cancer has taken over from lung cancer and is now the most common cancer in the UK and one of the leading causes of death in women.

The rationale for discussing inflammatory breast cancer (IBC) is that this disease is not easily detected and is therefore nicknamed the ’silent killer’. It is relatively rare, far less studied and much more deadly than the common form of breast cancer. While common breast cancer now has an 80% survival rate, only about 20% of IBC patients live more than 10 years after diagnosis. It is arguably the most feared by women because of the need to undergo numerous distressing chemotherapy treatments prior to the disfiguring surgery, mastectomy.

Inflammatory breast cancer is named after its characteristic initial symptoms, which include redness, warmth, and swelling of the skin of the breast. It is an aggressive form of invasive breast cancer that is not usually detected by mammograms or ultrasounds. It does not typically grow as a confined lump that can be felt in the breast, but instead grows diffusely in nests or sheets with not much mass. The symptoms, which have the appearance of an infection or inflammation, are caused by cancer cells growing along and blocking the lymph vessels in the skin of the breast. The breast becomes inflammed and swollen as the body reacts to the cancer cells in the lymph vessles. Inflammatory breast cancer has very poor prognosis and an extremely high risk of recurrence. Since it has often progressed before diagnosis, treatment is aggressive and extensive, including surgery, chemotherapy and radiation therapy.

It accounts for just 1-9% of breast cancer cases; however, because it resembles an infection rather than a typical cancer, many doctors try to treat it with antibiotics. IBC is therefore often misdiagnosed at first, causing patients and physicians to lose valuable time to treat the aggressive cancer. Since it is the most lethal form of breast cancer, and given that it is often misdiagnosed as another medical condition, early diagnosis is crucial in lowering mortality rates. This is why the use of nanotechnology could be invaluable in its diagnosis, treatment and prevention.

Currents methods used in the diagnosis of inflammatory breast cancer tissue

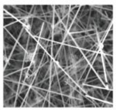
Mammograms are not effective imaging tests for inflammatory breast cancer but it may show thickened skin and increased breast density. MRI (magnetic resonance imaging) can find breast tissue that is cancerous and also allows skin changes that are typical of inflammatory breast cancer to be measured precisely. PET (positron emission tomography) / CT (computed tomography) scans are used to find cancer cells that have spread to nearby and distant lymph nodes, which are among the most common sites of inflammatory breast cancer spread.
Inflammatory breast cancer can also be diagnosed with a skin biopsy.

In vitro diagnosis of cancer cells has been done using gold nanoparticles and quantum dots. Optical imaging, using gold nanoparticles has limited applications in human studies as their optical signal is not very strong.

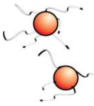
The ultimate goal in diagnosis is to identify the disease at the earliest possible stage. Explored below are proposals for future diagnostic techniques.

Possible future of nanodevices in detecting malignant cells in breast tissue

Inflammatory breast cancer diagnosis can be simplified and accelerated using nanotechnology.



In the future it may be possible to engineer **gold nanofibres**, that ‘stick’ to cancer cells when sprayed on the surface of the skin and light up for easy identification. These gold nanofibres decorated with hydroxyl groups, will strongly hydrogen bond with hydroxyl groups on neighbouring gold nanofibres forming a fine mesh. In this way full coverage of the breast is possible. In addition, by binding each gold nanofibre to an antibody for the protein found in cancerous breast skin tissue, it is possible for the gold nanofibres to be selective and stick only to the cancerous cells. Then by shining white light onto the breast tissue, any suspect cells can be easily identified as they will glow due to light stimulation. The advantages of this method are that cancer cells on the surface of the skin can be detected instantaneously, allowing early diagnosis, it is non-invasive and the procedure is not toxic to healthy human cells. As a result, there is no time wasted to find out if a person has cancer and treatment can start immediately, which could save lives.



Another promising approach in diagnosis would involve the design of spherical **nanobubbles** with tiny pores and filled with a fluorescent protein. The sphere has the largest volume to surface area ratio and the nanobubble would therefore contain more fluorophores than any other 3D shape. Again by conjugating the nanobubble with a targeting ligand, the nanobubbles bind only to the cell membrane of cancer cells. Upon binding, the nanobubble will burst and the fluorescent protein molecules will infiltrate cancer cells and interact chemically with the breast cancer protein with little or no interference with other proteins in cells. These cells can be detected in needle biopsies of breast tissue using a spectral imaging microscope. Malignant cells can be identified among healthy cells because they emit a specific colour of light in the visible region of the electromagnetic spectrum when UV light is shone on them. These novel nanobubbles are hoped to make imaging brighter and more informative. A further step to this approach is to make the cancer diagnosis sooner by the oral or intravenous administration of a buffered solution of these nanobubbles that also entrap a powerful light-generating system. This system triggers light production only after the nanobubbles have been taken up by the targeted cells. In this way distinctive images of the diseased tissue are produced and cancer cells can be identified *in-vivo*. A more advanced modification of this method would be the design of injectable nanobubbles that serve as contrast agents. These future nanodevices would target cancer cells and enhance their visibility, which would improve the resolution of cancer to the single cell.

Current methods of treating Inflammatory Breast Cancer and its disadvantages

Inflammatory breast cancer is currently treated by surgery, chemotherapy, and radiation therapy.

Mastectomy, where the entire breast and the lymph nodes under the arm are removed has been known to increase the chance of recurrence because inflammatory breast cancer involves the lymph nodes of the skin and the skin is stitched together after mastectomy.

Chemotherapy involves treatment using drugs and is often given before surgery to reduce the size of the tumour and decrease the risk of recurrence. These drugs affect all rapidly dividing cells. Therefore chemotherapy is not specific to cancer cells and has the potential to damage healthy tissue.

Radiation therapy involves the use of ionising radiation. It is given after chemotherapy but before surgery to kill cancer cells and shrink the size of inoperable tumours so that surgery can be done. It may also be given after surgery to reduce the risk of the cancer coming back. However, radiation therapy also affects healthy tissues by damaging its genetic material.

The current methods of treating inflammatory breast cancer are painful, time consuming, breaks down a patient's emotionally well-being and risk damage to normal tissues or incomplete eradication of the cancer. Nanotechnology offers the means to aim treatment directly and selectively at cancerous cells.

Nanoparticles used in the treatment of cancer

Nanoparticles have remarkable potential in cancer treatment. This is because they can interact with cells and tissues at a molecular level with a high degree of specificity, due to their very small size. This allows an association between technology and biological systems at a level that was not previously possible. With nanotechnology, cancer treatment can be less painful and more effective which would make the treatments less stressful for the patient.

The treatment of cancer using gold nanoparticles has used photothermal therapy for the destruction of cancer cells. When irradiated with focused laser pulses of suitable wavelength, targeted gold nanospheres, nanorods, nanoshells, and nanocages kill cancer cells.

Although inflammatory breast cancer responds to chemotherapy treatments, there have not been effective targeted treatments for this type of aggressive breast cancer where healthy cells are spared. The use of nanotechnology to design drug delivery capsules that target specific cells and unload large doses of poisons into malignant cells, while sparing healthy cells would eliminate the unpalatable side effects that accompany current cancer therapies.

Possible future of nanodevices in delivering potent drugs and killing malignant cells in breast tissue

In the future it is possible to engineer 'drug delivering' **nanodrums** that are administered orally. These nanodrums can be tailored to deliver precise doses of two or more therapeutic drugs to specific cancer cells at the target site. They can also be adapted to encapsulate therapeutic drugs with diverse physical properties such as hydrophilic and hydrophobic character or drugs with different charges on them. In this way, different receptors present only on the cancer cells will be bonded to, opening the way for combination drug therapy. A further modification of the nanodrums would be to devise a method to control the rate at which each drug is released once it enters the tumour cell. This then would be a way forward to personalise doses and treatment for individual patients depending on the stage of the cancer.

Fine tuning the design even further, these nanodrums would report the progress of the cancer and optimally deliver medication for treating, pain, nausea, loss of appetite, depression, difficulty breathing **-** conditions that arise with chronic anticancer therapy. This development would enhance the lives of individuals where the inflammatory breast cancer has spread to an inoperable level.

Another plausible method of treating inflammatory breast cancer in the future is to intravenously inject a buffered solution of **nanobullets** which will home in on cancerous cells, inject their poisonous cargo and kill them instantly. The nanobullets contain the nanoparticulate toxin and is bathed in a chemical that extends their life and enables them to travel undetected in the bloodstream until it reaches it target site and eradicates the ‘rogue’ cells. Since the toxin is encapsulated in the nanobullets, healthy cells are left unharmed and there is no systemic toxicity. These nanobullets are conjugated to antibodies that recognise antigens on cancerous cells enhancing the ‘homing in’ mechanism. These nanobullets could improve the effectiveness of chemotherapy, bypassing normal, healthy cells and minimising the side effects seen with these drugs.

The ultimate nanotool for inflammatory breast cancer, a disease that progresses so fast and seems metastatic from its inception would be the multifunctional **nanovac**. It is feasible that this device delivers and unloads anticancer vaccines to breast tissue and prevents the development of inflammatory breast cancer in high risk individuals. A microchip could be integrated to the nanovac and provide the possibility of monitoring *in-vivo* activities of cells by an external device. The nanovac would circulate freely in the blood and can be reprogrammed on removal and enable a change of strategy if the cells encountered are malignant.

Social and ethical issues concerning nanotechnology

Although nanotechnology can provide enormous benefits for medicine, such as selectively targeting specific cells and reducing the need for invasive surgery, it poses social and ethical issues. Due to the high accuracy and sensitivity it provides, future nanomedical diagnostics will heighten the awareness of an individual's health status. This may lead to psychological effects such as paranoia about one's own health and bodily functions that is unwarranted. Another issue to consider is whether the poor will get equal access to nanomedicine. If nanotechnology is not offered by the NHS, then only the rich will receive the benefits of this advancement and this can be deemed unfair. As nanomedicine is a relatively new advancement in technology, there is a lack of knowledge on adverse effects. Toxicity is a main concern and patients have to be informed about potential long-term consequences, if they are to use these devices.

CONCLUSION

The discussion in this paper reveals the enormous potential of nanotechnology in the diagnosis, treatment and prevention of inflammatory breast cancer. Much of the theoretical research described in this paper relies on the design and development of nanodevices that enable early detection of inflammatory breast cancer on the surface of the skin and those that enhance the visibility of cancer cells to the finest detail. Nanoparticle devices also facilitate the delivery of therapeutic drugs that aid in the management of the disease at a personal level, as well as toxins that kill cancer cells at their source.

Prevention of the disease is also possible in high risk individuals by the creation of nanoparticulate vehicles that deliver and unload anticancer vaccines.

A disadvantage of these methods is that the production of these nanodevices may require the use of highly toxic chemicals and corrosive substances. This would raise concerns on the environmental impact of the methods suggested. There is also the possibility that the biological pathway of the medicine malfunctions, and it is directed to the wrong part of the body such as the brain, leading to serious adverse consequences. To overcome these limitations, further research would need to be carried out to trial and improve nanodevices before they can bring about their beneficial impact.

Despite the limitations of the nanodevices, it is evident that a lot more research needs to be carried out on inflammatory breast cancer to drastically improve the lives and emotional well being of those at risk. Many individuals are deeply shocked and completely broken to discover how rapidly the cancer has metastasised. It would be in their interest to use nanotechnology to find ways to prevent the onset of this dreaded disease.

REFERENCES

1) A snapshot of nanotechnology http://www.cancer.gov/PublishedContent/Files/aboutnci/servingpeople/snapshots/2010_nanotech_508.pdf

2) Cancer Research UK http://info.cancerresearchuk.org/cancerstats/incidence/commoncancers

3) Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction http://www.pnas.org/content/102/33/11600.long

4) Caruthers S.D., Wickline S.A., Lanza G.M. (2007) Nanotechnological applications in medicine. In Current Opinion in Biotechnology 18(1), 26-30.

5) Development of Multifunctional Nanoparticles for Targeted Drug Delivery and Noninvasive Imaging of Therapeutic Effect www.bentham.org/cddt/sample/cddt6-1/004AR.pdf

6) Gold nanoparticles may simplify cancer detection; Science Daily http://www.sciencedaily.com/releases/2005/05/050509171246.htm

7) InflammatoryBreastCancer/inflammatory-breast-cancer
http://www.cancer.org/Cancer/BreastCancer/MoreInformation

8) Luminescent quantum dots for multiplexed biological detection and imaging
http://www.microbiology.emory.edu/.../Chan.02.COBiotech.13.40.pdf

9) Mail Online: The 20 most common cancers
http://www.dailymail.co.uk/health/article-105932/The-20-common-cancers.html

10) Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer
http://cancerres.aacrjournals.org/content/65/12/5317.full.pdf

11) Nanoshells as cancer therapy
http://www.understandingnano.com/nanoshells-cancer-therapy.html

12) NCI Alliance for nanotechnology in Cancer
http://nano.cancer.gov/learn/understanding/nanotech_nanoshells.asp

13) The ethics of nanotechnology
http://www.actionbioscience.org/newfrontiers/chen.html

Image References

1) Picture on title page: Courtesy of Paul Trombley, University of Michigan CBN, from Cancer Nanotechnology
http://nano.cancer.gov/objects/pdfs/Cancer_brochure_091609-508.pdf

2) Nanoshells as cancer therapy;
http://www.understandingnano.com/nanoshells-cancer-therapy.html

3) Size of nanoscale devices
http://www.cancer.gov/PublishedContent/Files/aboutnci/servingpeople/snapshots/2010_nanotech_508.pdf