

**NANOTECHNOLOGY – HAS CANCER FINALLY MET ITS
MAKER?**

**THE DEVELOPMENT OF CANCER NANOMEDICINE AND
ITS POTENTIAL IN THE NHS**

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PASS WITH MERIT

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ABSTRACT:

Throughout this paper I will highlight the advances in nanotechnology's application in the detection and treatment process of cancer. Specifically, the use of quantum dots and nanowires in diagnosis will be examined. This is alongside gold nanoshells' ability to target malignant cells, and when used in conjunction with photothermal ablation, capability to treat cancer.

Ultimately, I will then address to what degree the developing field of cancer nanomedicine will impact upon the standard of healthcare offered to the general public, through the NHS. It will become transparent that the use of gold nanoshells, QDs, and nanowires, have potential value as treatment and diagnostic tools, however, as they will not necessarily be deemed viable according to NICE standards, due to their inaccessibility, they are unlikely to have such a great impact in oncology as currently expected.

INTRODUCTION:

What are the funding issues currently faced by the NHS?

Since its conception, the National Health Service's forefront principle has been the idea that treatment should be 'free at the point of contact'. This standard has allowed healthcare to be made available to anybody who needs it, regardless of their affluence.

Countless forms of healthcare are covered by this, from GP consultations and the appropriate treatment for a verruca, to organ transplantation surgery, the necessary immunosuppressant drugs and lifetime aftercare with a specialist consultant.

The NHS treats a vast numbers of patients, approximately 8 every second. Although there are now charges for some prescriptions, as well as dental and optical care, the service remains true to its mantra and, in the main, does not charge.

The result; the NHS has grown to become the world's largest publicly funded health service.

However, the NHS's enormity, and the impact it has on society's health, is directly proportional to its operating costs. In 2008/9 the NHS's budget was over £100billion and there is an average increase in spending of approximately 4% a year, however, £20 million efficiency cuts loom.

What is NICE?

As patients expect new and innovative drugs to be made available as science advances, guidelines set by the National Institute of Clinical Excellence, the NHS regulating body, look set to stand in their way, as the definition of 'cost effective' medication looks set to change in these austere times.

The National Institute of Clinical Excellence, abbreviated to 'NICE', provides guidance and sets quality standards on behalf of the NHS. It often makes recommendations on 'new and existing medicines, treatments and procedures', with

the aim of cutting costs while maintaining, or even improving, the standard of healthcare being offered.

Recently NICE have come under fire on a number of occasions regarding the treatment of cancer, most notably in the case of Barking and Dagenham PCT rejecting 37 year old Nikki Blunden's request for £25,000 a year cancer drug *lapatinib*, in line with NICE guidelines.

Unfortunately, as the nation tightens its belt, this is a trend that looks set to continue for the foreseeable future.

What is Nanotechnology and Cancer Nanomedicine?

In layman's terms, nanotechnology is the 'engineering of functioning systems at the molecular scale', relating to the prefix, 'Nano', meaning "dwarf" in Greek. Nano is also shorthand for nanometer, one-billionth of a meter.

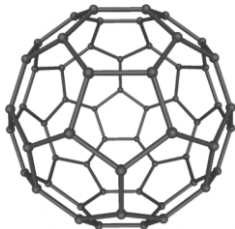


Fig 1

Nanotechnology was first given time on the global scientific stage when Richard Smalley and colleagues discovered the 'Buckyball' (**Fig 1**) in 1985. Buckyballs, the full name being buckminsterfullerenes have been investigated in depth due to the interest in their unique chemical properties, and subsequent

possible applications in nanotechnology. It was this discovery that sparked further study into the field. In 1996 Smalley and 2 other researchers won the Nobel Prize for chemistry for the breakthrough.

Products already on the market containing nanotechnology include sunscreen, containing nanoparticles of zinc oxide that allow it to rub on clear, stain resistant clothing and antibacterial dressings that use nanoparticles of silver that do not allow microbes to partake in cellular respiration.

In terms of investment in the field is booming with the U.S. government alone allotting more than one billion dollars towards nanotechnology in 2005 which is more than twice what was spent on sequencing the human genome when at its pinnacle. The National Science Foundation estimates that the speciality will be worth over a trillion dollars by 2015.

Cancer nanomedicine is the umbrella term used in reference to nanotechnology and its medical application in the diagnosis and treatment of cancerous cells.

Research is continually being carried out to establish whether cellular machines operating at the nanoscale level are capable of such a feat, and so far many different variations upon this area of interest have shown promising results in the battle against cancer, with an estimated 130 nanotech-based drugs and delivery systems being developed worldwide.

It is expected to change the very foundations of cancer treatment, diagnosis and detection.

DISCUSSION:

Cancer diagnosis at present:

To have a tool of diagnosis that would allow the early detection of cancer is a tantalising idea, especially when it is considered that currently employed diagnostic techniques such as medical imaging, tissue biopsy and bioanalytical assay of body fluids are insufficiently sensitive and specific to detect cancer at its earlier stages. In fact, in most cases these methods are only able to pick up on tumours when they have reached such a size that, more likely than not, the tumour has already metastasized. At this stage it is naturally far more difficult to treat.

Nanotechnology as applied to cancer *diagnosis and detection*:

Nanowires

Nanowires are defined as structures of a nano-scale, in that they are no more than a few 0.000000001m in diameter. They can be made from a number of materials from which they gain their status as either metallic, semi-conducting, insulating or molecular.

Research is currently examining their application to medicine in the detection of cancer. Because cancer does not induce the production of specific antibodies that can be detected undeniably with appropriate blood testing, it is far more difficult to recognise it in its earlier stages, before clear-cut symptoms present themselves.

It is generally regarded by scientists that these nanowires may be able to solve this problem. Cancer causes a change in the number and type of proteins that circulate around the body in the blood - nanowires have the potential to detect these protein molecules, as well as other biochemical markers of cancer.

Identifying cancers through a method similar to this, when they only consist of a few thousand cells, would make them far easier to treat than at later stages, and would result in a reduced impact on a patient's quality of life if treatment need not be so intensive.

A paper in the journal Nature Biotechnology details how researchers at Harvard University have conducted investigations using silicon nanowires to sense these markers of cancer even when they equal only "one hundred-billionth of the protein present in a drop of blood". Not to mention the unbelievable accuracy and sensitivity of the nanowires, they also have the capability of recognising the type of cancer present far sooner than in oncology currently.

The research involved linking slender nanowires that conducted a small current with receptors for certain markers of cancer including prostate specific antigen (PSA), PSA-a1-antichymotrypsin, carcinoembryonic antigen and mucin-1.

When these proteins come into contact with a receptor, it triggers a momentary change in conductance that can be subsequently measured and be used to diagnose. They are able to differentiate among different cancer markers because of two features, 1) the receptors they combine with are specific to each biochemical, and 2) each binds to its receptor for a distinguishing length of time before coming loose.

Experiments have also been carried out using nanowires with nucleic acid receptors for telomerase, an enzyme that remains inactive within healthy body cells, but becomes active in over 80% of cancerous cells.

Jim Heath, a chemist at Caltech, using this method has now succeeded in installing many thousands of these nanowires, acting as sensors, into a detection chip. His reports conclude that the chips can currently label 20-30 biomolecules. It is his ultimate aim to develop a test that would label 20 forms of cancer, a feat requiring approximately 500 measurements – 20-25 different biochemical for each cancer.

While initial rounds of cancer testing today identify only whether or not cancer is present, nanowire technology has the promise to not only uncover what type of cancer is present, but could also be used track patients' progress throughout their course of treatment – blood could be tested quickly and precisely, without the need for biochemical manipulation that there is currently.

Quantum Dots

Quantum Dots, or QDs, are semiconducting nanocrystals that have a standard diameter of between 2-8 nm. Interest has arisen from their potential for use in medical imaging due to their unique luminescent, optical and electronic properties, for which the quantum confinement effect is responsible. Such properties, especially their reduced tendency to photobleach (thus limiting complication during the observation process), make them suitable in the detection of cancer biomarkers.

In vivo:

QDs are regarded as being of use in in-vivo imaging. Some of the first research on this topic was published in Science and carried out by Dubertret at Laboratoire D'Optique Physique. Quantum dots contained within a phospholipid sphere were injected into frog embryo cells – the researchers were able to watch the embryos develop over a 5 day period. According to this research QDs are stable, non-toxic and are highly resistant to fading under constant illumination in vivo.

Since, researchers have started to use quantum dots for in vivo imaging in laboratory animals, formulating dots to image tumours. To do so, biocompatible quantum dots are being developed that fluoresce in the near-infrared region of the spectrum. This will provide greater sensitivity as well as better resolution in vivo.

In identification and multiplexed analysis:

Quantum Dots have already been proven to be able to identify live breast cancer cells by the Quantum Dot Corporation and Genentech. They made use of QDs joint to immunoglobulin G (IgG) and streptavidin to label the Her2 cancer marker present on the surface of live breast cancer cells.

QD have also been demonstrated to have the ability of carrying out multiplexed analysis, i.e. a procedure that simultaneously measures multiple analytes in only one assay.

In cancer of the prostate it is prostate-specific antigen (PSA) serum level that is currently used in screening. However, a report by Laxman and Morris concluded that the test 'lacks ideal specificity' and that additional biomarkers were needed to supplement this indication in order make a more definite diagnosis. They conducted an experiment involving a multiplex panel, measuring seven prostate cancer biomarkers with analysis confirming that this multiplexed model outperformed serum PSA or PCA3, a noncoding RNA transcript, alone in detecting prostate cancer

QDs have been demonstrated to be able to partake in multiplexed analysis by

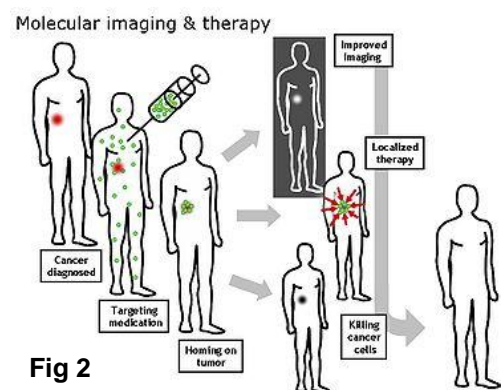


Fig 2

Goldman, and accompanying research team.

They revealed how four different QDs, of different wavelengths, could analyse four toxins in a single immunoassay. The capability of QDs to take such an approach would thus allow the simultaneous identification of many biomarkers and when used in the detection of cancer, would result in more reliable and effective diagnosis.

Other uses of Quantum Dots:

Quantum Dots are also being investigated for their potential application to targeted drug delivery systems as well as in medical imaging (**Fig 2**). Shuming Nie alongside other researchers at the Nie Lab Research Group at Emory University, are developing QDs that can be conjugated to peptides or antibodies in order to target only human tumour cells that are being grown, for experimental purposes, in mice. Another method has been to encapsulate QDs in amphiphilic polymers and then bound to tumour targeting ligands. The use of such a system would allow only specifically targeted cells to receive the drug, thus minimizing any side effects in the same way as gold nanoshells.

Cancer treatment at present:

At present there are many alternative cancer treatments including drugs and surgical procedures, alongside chemotherapy and/or radiotherapy. However, not only are these treatments not guaranteed to improve upon the patients state and cure them of the cancer, they cause patients to become subject to a number of unpleasant, and quality of life decreasing side effects including anaemia, alopecia, and fertility problems.

Nanotechnology as applied to cancer treatment.

Gold Nanoshells:

Long have gold nanoparticles been used in medical studies, with investigations into the merit of colloidal gold, a solution of golden nanoparticles in liquid, in treating rheumatoid arthritis dating back to 1927. Lagophthalmos, the inability of a person to close their eyelids, has also been treated by the implantation of a small amount of gold into the upper eyelid.

Then came the birth of Gold nanoshells, the idea of which was introduced in the 50's but was not put into practice until the mid-1990's by researcher Naomi Halas of Rice University, with Houston-based biomedical firm Nanospectra Biosciences beginning the first human clinical trial of nanoshell phototherapy in 2008.

The nanoshells themselves are either hollow or with a non-conducting core, spherical in shape with an inner lining of silica, an outer of gold and a diameter between 20-70 nm. By varying the size and thickness of the spheres they can be modified in order to respond to light from the nIR, the near infrared spectrum. Because light from this spectrum can be passed through the body without causing harm, the shells can be heated whilst inside the body which will result in no aesthetic impact as well as no pain or discomfort.

Researchers at UC Santa Cruz have experimented with skin cancer in mice to demonstrate the potential of gold nanoparticles (HAuNS) to 'burn' melanoma in a process called photothermal ablation.

As published in Clinical Cancer Research, a peptide, polyethylene glycol (PEG) attached with α -melanocyte-stimulating hormone (MSH), was used to bind to the nanoshells and guide them to a melanoma, working in this way as a targeted drug system (**Fig 3**), the nanoparticles specifically being taken up by melanoma cells. A nIR

beam was then used to 'burn' it, and it did so without causing considerable damage to

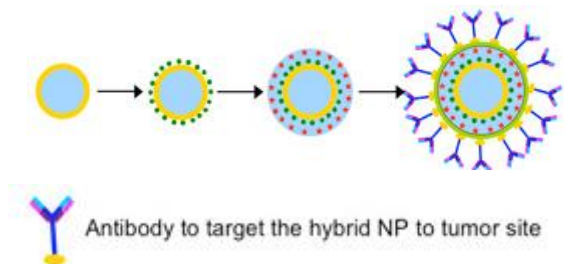


Fig 3

non-cancerous cells in the vicinity.

Scientists at Rice University and at Baylor College of Medicine, working in conjunction with Texas Children's Hospital, have also successfully used gold nanoshells in the treatment of a specific form of brain cancer.

The results of the study, published in the Journal of Neuro-Oncology, reported that more than half of the mice that received the nanoshell treatment for glioma tumours had no indication of cancer more than 90 days after treatment. This is particularly impressive given that glioma is among the most aggressive and difficult-to-treat of all brain cancers, with procedures being highly invasive and subsequently, sometime inoperable. Advances in such a treatment would therefore be of significance as it would greatly improve a patient's chances of survival as currently, fewer than five percent of patients survive beyond five years

The researchers injected the mice with nanoshells and waited 24 hours for the nanoshells to congregate in the tumours. Because the gold nanoshells are only approximately 120 nm in diameter they are small enough to move into the rapidly grown, and subsequently not fully developed blood capillaries and so become lodged in the tumour. The fact that they only lodge in tumours means that the treatment would be far more efficient and cause far fewer side effects, especially when compared to chemotherapy and radiotherapy which can cause nausea, radiation recall and alopecia.

A laser of near-infrared light was then positioned over and aimed at the tumour for three minutes. The nanoshells then caused the light energy from the laser to be transformed to thermal energy, the heat from which severed the adjacent cancerous cells. All seven animals that received the nanoshell treatment responded, but cancer returned in three. The other four remained cancer-free 90 days after treatment.

Although testing is only into its first round, the results suggest that photothermal ablation using nanoshells may one day be a viable option for glioma patients. However, it must also be considered that this procedure was only tested upon 7 mice, in 3 of which the cancer returned within the 90 day time frame.

Another point in favour of this treatment is that because it enables the cancer to be treated in early stages which means the cells are less likely to have mutated and become resistant to cancer medication, which may be used together with this technique. At present, because cancer adapts so rapidly medication is rarely able to keep up.

Follow up work will be needed before clinical trials on humans may begin but already further research is being carried out at Rice, and other institutions, to develop similar nanoshell based treatments for pancreatic and prostate cancer.

But will they be considered by NICE?

There appears to be many positive points in the use of different forms of nanotechnology to treat cancer, it therefore makes it very easy to overlook the fact that the science does not come without its problems. Nanotechnology has been proven to not always be beneficial to human health; this together with factors concerning research and 'cost-effectiveness' implications, this could impact a decision made by NICE whether or not to approve it. These concerns include:

1. Incomplete research.

Although first-stage experiments and animal trials have shown promise in these techniques for use in the fight against cancer, it must be bared in mind that none of these treatments or diagnostic techniques have yet been trialled on humans. The anatomy of a frog or a rat is relatively far removed from a human's, and so the results gained in these trials may not be consistent with results from trials on people.

2. Disagreement in research.

There is undoubtedly now a better understanding of what kinds of peptides, proteins, and other biological molecules that can be combined with the nanoparticles to target only cancer cells; however, there appears to be some disparity on the standard size, shape, or composition of those nanoparticles. This should be regarded with significance as even small alterations in the dimensions of a nanoparticle can affect the way in which it acts whilst in the body. This may cause it to become non-functioning, but more ominously, it may also result in it doing more harm than good.

3. The toxicity of nanoparticles.

In 2004 toxicology reports found that largemouth bass, exposed to water containing Buckyballs at a concentration of 500 parts per billion, suffer brain damage. This information should be seen as particularly troubling as it could mean that humans are similarly vulnerable, further investigated at Rice University. Chemist Vicki Colvin found that after she had exposed lab-grown human skin and liver cells to a *less* concentrated solution of Buckyballs, 20 parts per billion, half the cells died.

This also raises the question of how safe are the products already on the market that contain nanoparticles. Some evidence has already been compiled, that the nanoscale particles of titanium dioxide used in sun cream can form highly reactive free radicals when exposed to sunlight. These free radicals could damage cells, potentially causing them to become cancerous.

If NICE felt that the use of nanotechnology in medicine would have a much lesser beneficial impact than it would a damaging one, it seems unlikely that it would even be seriously considered. However, recent studies have suggested that Buckyballs could be made less toxic fairly easily, thus instilling hope for other nanoparticles. By attaching hydroxyl groups the Buckyballs became less dangerous, those with the most hydroxyl groups', safe exposure level going up by a factor of ten thousand.

Also, the health implication of nano-scale technology has been assessed by the Royal Society and Royal Academy of Engineering. Although a report concluded that 'uncertainties about the risks of manufactured nanoparticles need to be addressed', they rejected the need for a delay in the development of nanotechnology that was called for by the ETC group. It was decided that ingredients in the form of nanoparticles should undergo full safety assessment before being commercialised, however, if treatment and diagnosing techniques using nanoparticles did succeed in meeting this criteria, there should be no reason as to why NICE should reject it on the grounds of health and safety.

4. Would it be cost effective compared to current practices?

In terms of diagnosis when the use of QDs and nanowires are compared to assays that are used at present, QD's are shown have rapid detection that is easy to carry out, thus providing quick point-of-care screening. They are also able to carry out multiplexed analysis, whereas assays are a time consuming, labour intensive and expensive procedure.

Yes, the use of QD's or nanowires in cancer diagnosis will at first probably be quite expensive, an assumption being made on the idea that new technologies *are* usually more expensive, (as no pricings have been released, or even estimated due to their continuing development). However, when it is considered that both nano-scale systems can make use of multiplexed analysis, these techniques are likely to prove more cost effective than regular assays due to the sheer number that must be done in order to establish the same amount of information QDs and nanowires can provide in one test.

In terms of treatment the outlook is rather less positive in regard to cancer nanomedicine being given the go-ahead by NICE. When the seven most common forms of cancer in the UK, including Breast and Prostate cancer have a survival rate of greater than 50% using current treatments, it seems unlikely that NICE would invest in something new unless it was particularly cost effective. This is supported by NICE's rejection of cancer drug lapatinib for women with advanced breast cancer in 2009, despite it showing considerable success. It cost £25,207 a year and so it was not deemed viable in spite of it being effective.

Therefore, if a nano-scale treatment such as the use of gold nanoshells used with photothermal ablation was proved to be effective in clinical trials but had a hefty price tag, it seems ever more unlikely, especially because of forth-coming cuts, that a nanomedicine will be integrated into the NHS any time soon.

CONCLUSION

Nanotechnology's application to the medical treatment of cancer has thus far been shown to be a success as inferred by the trial and experiments I have featured in this

paper. If this trend were to continue throughout clinical trials on humans, problems being ironed out and it being deemed safe to use, then the potential impact it could have would be momentous. However, unless these treatments could be developed in such a way to minimise the commercial cost, despite their effectiveness, they would have no effect on the vast majority cancer patient's treatment in that it would only be available to a select few who could afford to use the private sector. If this were the case, the NHS could not justify spending such a great amount of money when they have to care for so many other people, with so many different afflictions.

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