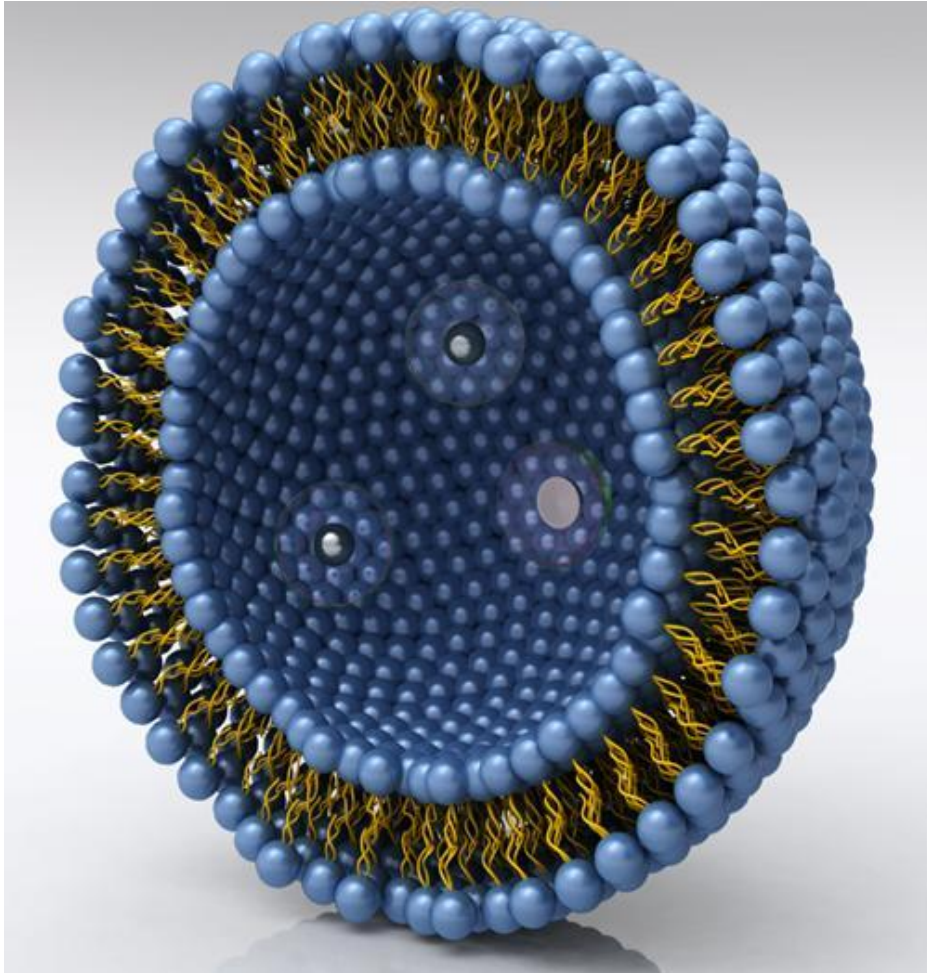


Nanotechnology Uses in Cancer Treatment and Diagnosis, as an  
Alternative to Existing Methods.



By  
Jack Yon

PASS WITH MERIT

Research Paper  
Based On  
Pathology Lectures  
At Medlink 2010

## **Abstract**

Current treatments for cancer all have large health risks attached to them. For example in chemotherapy, the relatively non-specific drugs are toxic to most cells and are not localised to the site of the tumor. The damage is evident even from the outside by the loss of hair. Treatments such as radiotherapy, while slightly more targeted, are highly dangerous and cause serious damage to the area being targeted, including fibrosis and in rare cases, a second cancer caused by radiation.

Nanoparticles, however, have the potential to offer targeted treatment with decreasing damage to surrounding tissue. Cancer therapies including dendrimers, nanocapsules and gold nanoshells all show great promise in both targeting and treatment of cancer. This paper highlights the current successes of nanomedicine in oncology and discusses its potential in the future, as a safer, more effective alternative.

## **Introduction**

Cancer is one of the biggest killers in the UK, it accounted for roughly 30% of all males and 25% of all females who died in 2007. According to Cancer Research UK, over 298000 people were diagnosed with cancer in the UK in 2007. Roughly 130 women every day are diagnosed with breast cancer. The lifetime risk of being diagnosed with breast cancer is 1 in 8.<sup>1</sup>

About £5.1 billion is spent per year on cancer treatment by the NHS. However this is really not enough to treat such a prolific killer. Overall, the cost of cancer to the government in treatment, time off work, hospice costs, and other things such as informal care is £18.3 billion<sup>2</sup>. So it is clear that more effective treatments need to be developed.

Cancer can be classed as a disease in which a group of cells proliferate uncontrollably, commonly due to a malfunction in the genes which stimulate or repress growth of cells (known as oncogenes and tumor suppressor genes). A well known example of this is the Philadelphia Chromosome, which is genetic malfunction directly linked to chronic myelogenous leukemia. It is a result of the translocation between chromosome 9 and 22. The problems with cancer cells derives from their main characteristics: described in the

Hanahan and Weinberg paper on the "Hallmarks of Cancer"<sup>3</sup>

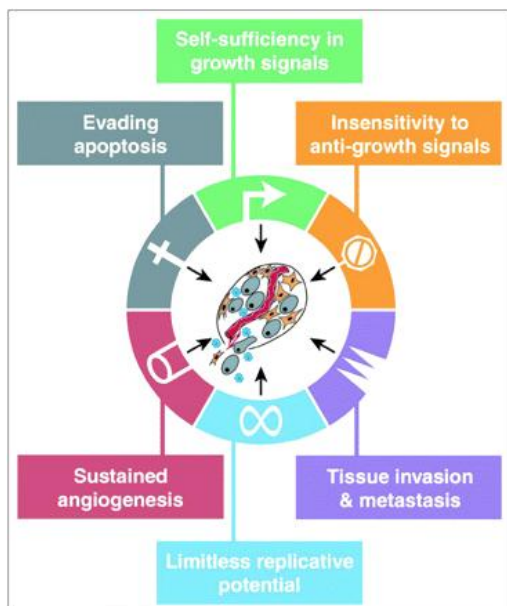


Figure 1- the hallmarks of cancer.

As shown in Figure 1, cancer is able to evade the body's mechanisms of malignant cell destruction and growth suppression, whilst growing new blood vessels to sustain it.

It can also move around the body and form secondary tumors (metastases) which in many cases are located in more life threatening areas than the original tumor, and often kill the host.

Finally, cancer has the ability to replicate infinitely, unlike normal cells.

Roughly 1 in 4 people who have cancer die from it.

This shows that there is still much more to be done in terms of treatment and diagnosis. A lot of current treatments all carry inherent risk factors, whilst often only extending the life of the patient by a matter of months. This leads to many ethical issues in cancer treatment.

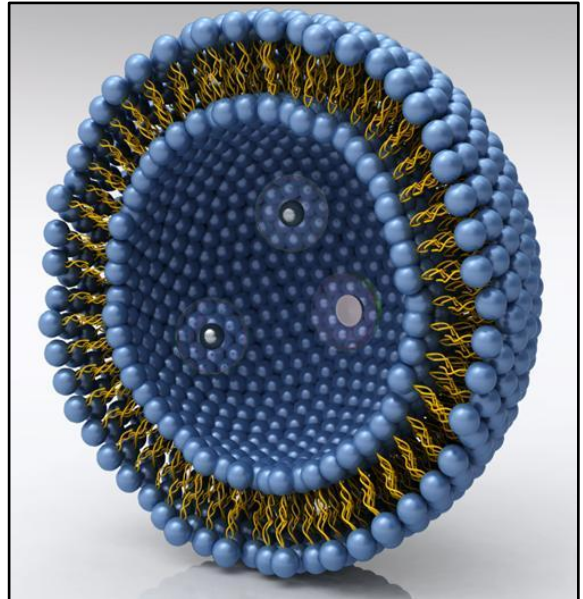
<sup>1</sup> <http://info.cancerresearchuk.org/cancerstats/types/breast/?script=true>

<sup>2</sup> [http://www.policyexchange.org.uk/images/publications/pdfs/The\\_cost\\_of\\_cancer\\_FINAL.pdf](http://www.policyexchange.org.uk/images/publications/pdfs/The_cost_of_cancer_FINAL.pdf)

<sup>3</sup> Douglas Hanahan and Robert A. Weinberg, Hallmarks of Cancer: The Next Generation, February 2011

So what are the alternatives? This paper proposes nanotechnology as the treatment of the future, as a safer and more effective way of treating cancer.

What is nanotechnology? Nanotechnology refers to molecules or molecular fragments, which have been engineered for a specific purpose, at the nanoscale. These objects are typically smaller than 100 nanometres, and often differ in chemical and biological properties when compared with the macroscopic material. They are similar in size to molecules such as enzymes, or short proteins<sup>4</sup>. This size makes the particles perfect for their function in medicine at a cellular level. These nanoscale devices can easily interact with cell surface membranes, or can penetrate the cell, and be engineered to interact with the cell surface receptors. Clearly from a medicinal perspective, a molecule that can attach to cells holds a vast array of potential, from drug delivery, to diagnosis, or even improvement of the successes of current therapies, when used in combination. Because these molecules operate at a cellular level, the amount of collateral damage can also be limited, making nanomedicine the safer option for patients with pre-existing health concerns. Also, despite the size of these molecules, they have the potential to carry thousands of small molecules, such as contrast agents for diagnosis, or an anticancer drug. Or even both, to operate as a nanoparticle that both diagnoses and treats the patient.



*Figure 2- A gold nanoshell, which would be used for potential cancer treatment.*

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<sup>4</sup> National Cancer Institute, Cancer Nanotechnology: Going small for big advances, NIH publication, Jan 2004

## **Discussion**

### ***Current research for nanotechnology in cancer diagnostics:***

Clearly when it comes to treating cancer, a rapid diagnosis is critical for effective treatment. Many nanoscale devices are being researched to detect cancer. The two most promising methods seem to be the use of nanowires or the use of cantilevers. Both use antibodies specific to certain markers (e.g proteins) released by cancerous cells. These biomarkers are an effective way of detecting cancer early. An example of a biomarker would be Her-2, a protein that acts as a growth factor receptor in breast cancer.

Nanowires are designed to detect the biomarkers of cancer (e.g breast cancer marker Her-2). They work by having wires roughly 1-2 nanometres wide, coated in antibodies specific to the tumor markers. If a marker binds to the antibodies, the conductivity of the device changes, which is an easily measurable physical quantity.<sup>5</sup> The implications of this being that if the nanowires were exposed to tissue fluid, blood or lymph, different markers would be detected by the nanowires, and then therapeutic action could be taken.

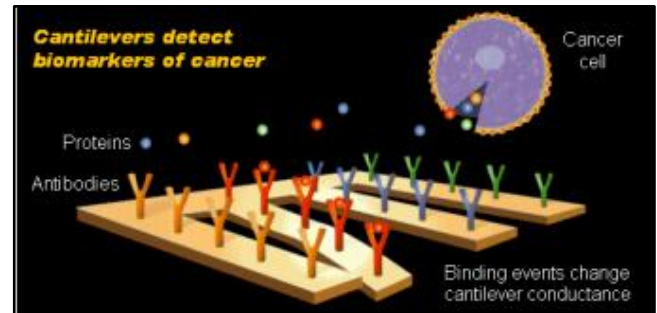


Figure 3- a cantilever.

Similar in concept, nanoscale cantilevers are also being researched. These involve a series of beams that can bend, which are then coated in either antibodies or DNA/RNA complementary to a specific gene, found in tumors. When a substrate binds (e.g a sequence of RNA), the beams bend, and this bending can be measured.

### ***Current research for nanotechnology in cancer therapeutics:***

Many nanoscale molecules (e.g gold nanoshells, dendrimers, micelles) have the potential to be chemically attached to drugs that release upon binding to the target cell (in this case, a cancer cell).

Drug delivery systems such as dendrimers are conjugated (attached to) antibodies specific to the cancer and may either contain or have attached a drug specific to the cancer cell that would destroy the cell.

The other most extensively researched method is the usage of gold nanoshells. These can be conjugated to antibodies, and then injected systemically into the patient. when they attach and therefore collect around the tumor, an electromagnetic wave in the near-infrared (nIR) spectrum is shone upon the target area. This light ( at a wavelength of roughly 800 nanometres) matches a particular absorbance frequency of the nanoshells. This causes them to heat up and literally burn the cancerous cells.<sup>6</sup>

### **Medicinal potential for gold nanoshells:**

These shells are a particularly fascinating area of research, due to the absence of any alternative drug being attached to them, limiting chances of adverse side effects or abnormal reactions to the drug. The burn damage is also limited to the tumor and the very limited amounts of cells surrounding them.

<sup>5</sup> <http://www.tahan.com/charlie/nanosociety/course201/nanos/NH.pdf>

<sup>6</sup> <http://singularityhub.com/2009/12/14/nih-guides-nanomedicine-towards-killing-cancer/>

The best part about the nanoshells which makes them so promising for future applications, is the type of light required to heat the nanoshells. There are no known side effects of the nIR radiation and is already used widely, such as by the medical physicists at Imperial College London. They use nIR light in spectroscopy to measure amounts of oxygenated haemoglobin, in their research into neonatal brain development<sup>7</sup>. This has been tested in hospitals and the nIR light appears harmless to living tissue, and passes through biological matter well enough to penetrate any part of the body, giving the nanoshells potential use around the whole body.

As such, these particles come across as the most

promising nanoscale therapy, because of their *in Vivo* viability (due to gold's low reactivity). They are also relatively easy to make<sup>8</sup>. The future of gold nanoshells is wide open due to their versatility.

On the 21-June-2004, the gold nanoshells were tested on mice<sup>9</sup>, with incredibly positive results. The group of cancerous mice was injected with the shells, and had nIR light shone on them. All signs of cancer disappeared after 10 days of treatment. There was no reoccurrence of the cancer. This treatment has actually entered clinical trials.

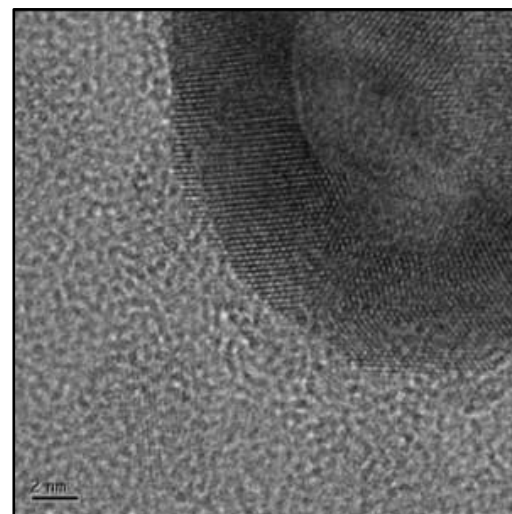
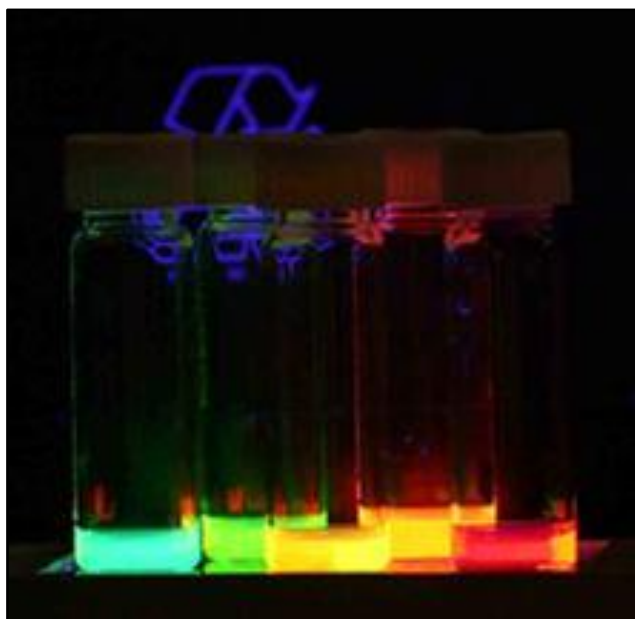


Figure 4- A Scanning Electron Micrograph of a gold nanoshell.



dots<sup>10</sup>. These are nanoscale crystals made of a material such as cadmium selenide.

Figure 5- Quantum dots irradiated with UV light, the different colours are present because of different sizes of dot, this effect is due to quantum confinement.

These crystals serve the purpose of being nanoscale sources of light, with colour varying with size, and would illuminate the tumor if bound to it.

A logical progression of nanoparticles such as dendrimers would be to combine many theories and lines of research, into one nanoparticle. The potential of a particle that could locate, highlight and

#### More promising developments for the future:

Some of the following developments are in research already, but some are just concepts. However they are all based on solid theory, and all show promise in becoming the future of medicine.

##### 1-Multi-functional nanoparticles:

As is evident, diagnostics and therapy are both in the spotlight at the moment, with nanotechnology being a tool for both. One other interesting development is that of quantum

<sup>7</sup> <http://www1.imperial.ac.uk/medicine/research/researchthemes/healthtechnologies/sensingdevices/nirs/>

<sup>8</sup> [http://www.nanoed.org/concepts\\_apps/AuNanoShells/InDepthIntroPg1.html](http://www.nanoed.org/concepts_apps/AuNanoShells/InDepthIntroPg1.html)

<sup>9</sup> [http://www.nanoed.org/concepts\\_apps/AuNanoShells/InDepthIntroPg1.html](http://www.nanoed.org/concepts_apps/AuNanoShells/InDepthIntroPg1.html)

<sup>10</sup> <http://www.azonano.com/Details.asp?ArticleID=1726>

simultaneously treat a cancer is almost limitless. For example, using current dendrimer technology, the dendrimer could be adapted to have antibodies, a quantum dot or fluorescing agent and a therapeutic drug attached to it, allowing for both the detection and treatment of the cancer simultaneously. Many permutations and combinations of technologies available would allow for different treatment styles. For example, a contrast agent could be used to highlight the tumor on a scan, and could also be attached to a drug that kills the tumor, reducing the size of the tumor or making it easy for the surgeon to find it and operate. It would also be ideal if a basic “template” anticancer nanoparticle could be created, which could then just have the specific antibody conjugated onto it at a later date, perhaps from a whole range of proteins that would have been pre-prepared. This would mean that therapies could be mixed and matched to produce the best results for any particular cancer. Multi-functional nanoparticles would be the future of in-hospital treatment, with doctors able to find the tumor’s location, and give a prognosis and formulate a further treatment plan, whilst the cancer targeting drug is already active, minimising the downtime in a hospital caused by waiting for lab results, because the preliminary treatment is already in progress.

This experiment has been done with a nanoparticle attached to a chemical called folate (which targets the folate receptor found on malignant cells), alongside a fluorescent chemical and an anticancer drug.<sup>11</sup>

### 2-Monitoring Systems:

In terms of prevention, a vaccine for all types of cancer is a long way down the line. However, a constant monitoring system could hypothetically be set up using either a diagnostic tool such as the nanowire or cantilever which could be enlarged to incorporate antibodies of all known cancer cells, and given in the form of a macroscopic implant, either subcutaneous (like the contraceptive implant or insulin pump) or deeper within the body (like a pacemaker). This could constantly monitor fluid samples, and alert the user to the presence of cancerous cells should they develop. This would allow doctors to not only be aware of the presence of cancer, but if calibrated correctly, could be used to determine which type of cancer.

Of course this technology could also be given to cancer sufferers, to monitor the progression of any treatment being given, if it was set up in such a way that it could monitor concentrations of the biomarkers, giving the doctor feedback on the effectiveness of the treatment given, and whether the patient is actually improving or if their condition is worsening.

It should be noted that this is not an incredibly abstract and fictional prediction, without any scientific basis. Research into nano-implants has been conducted in many fields<sup>12</sup>, such as the endocrine system, with hormones such as insulin for diabetics being a topic of interest, because a monitoring system that administers insulin automatically would remove the need for diabetics to monitor themselves<sup>13</sup>. Research into a different method of cancer monitoring has been undertaken at the Massachusetts Institute of Technology<sup>14</sup>

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<sup>11</sup> <http://www.tahan.com/charlie/nanosociety/course201/nanos/NH.pdf>

<sup>12</sup> <http://www.nanolawreport.com/2007/10/articles/nanoimplants-predicted-to-monitor-health-status/>

<sup>13</sup> [http://www.diabetesincontrol.com/index.php?option=com\\_content&view=article&id=2243](http://www.diabetesincontrol.com/index.php?option=com_content&view=article&id=2243)

<sup>14</sup> <http://www.zdnet.com/blog/emergingtech/a-nano-cancer-monitor-implant/440>

### 3-Indirect treatment:

There is research into a treatment for cancer that involves targeting the cancers supply of blood, rather than the tumor itself. As previously mentioned, one of the hallmarks of cancer is the ability to induce angiogenesis (the growth of blood vessels to supply the growing tumor). However a group of scientists used nanoparticles to deliver a gene that forces blood vessels to self destruct. This cuts of the blood supply to the tumor, killing it. This treatment is a perfect example of the uses of nanoparticles as opposed to traditional medicine, and will require more research in the future for an effective delivery system. But it is evident that without the availability of nanotechnology, this would not be possible because if the gene was applied to the whole body, we would die. It is only by the extremely specific and targeted nature of nanomedicine that this is possible.

### 4- Direct DNA repair:

It should technically be possible to target cancer at the cause, rather than treating the symptoms, or attacking the supply of the tumor. If the cancer is caused by a malfunction in a gene, or a sequence of genes, to cause unsuppressed growth, it should be possible to replace the faulty DNA with working DNA. The new strand could be joined to a dendrimer, then the dendrimer could be targeted to a cancer cell. This would not remove the tumor, but it would make it benign, so that no malignant metastases would cause damage elsewhere.

As shown in figure 6- dendrimers have had singular genes attached, but it should be possible to attach whole chromosomes, to replace faulty DNA in a cell.

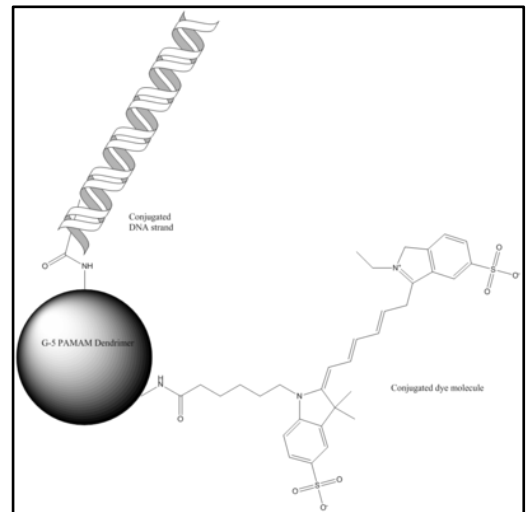


Figure 6- A dendrimer with a gene attached to it

## The Issues of Nanotechnology:

Although the downfalls of current therapies (e.g chemotherapy and radiotherapy) have been highlighted, it should be noted that they do also save lives every day. And that although nanotechnology could promise a better future for medical treatment of cancer, the full side effects are not known as of yet, and there are many factors that need to be considered.

First, there seems to be a misconception that nanotechnology is mainly concerned with building miniscule robots that will have conscious thought and the ability to achieve world dominance. For example, films such as "G.I Joe" have included nano robots as the enemy, and that they are capable of destroying anything. The film goes to the extent of using these nanobots to destroy the eiffel tower. However these notions should be disregarded, as the nanotechnology currently being researched in medicine is the use of molecules with properties determined by nanoscale alterations, such as the additions of antibodies. These molecules are not conscious and do not have the capacity to rebel. The other concern related to this concept is that such small but powerful tools will inevitably be turned to warfare, and that this could have devastating consequences.

However there are more real concerns attached to the use of nanotechnology, which must be considered in full.

There are concerns about the toxicity of some quantum dots due to their heavy metal composition, and there have been reports of cytotoxicity. There are also worries that these nanoparticles may be accumulated in the body, rather than excreted. Some research has shown that the non-biodegradable nanoparticles accumulate in the liver, so perhaps there are side effects. There is also a concern that the surface area to volume ratio of these molecules makes them incredibly reactive, and that this unexpected reactivity may cause damage to the body as well as the cancer cells. However the extent and gravity of these effects is as yet unknown, with more research needed before a conclusion can really be drawn about the health risks associated with nanomedicine. It can however be said that the potential benefit of these medicines is too great to warrant a lack of research, purely because of the potential side effects.

Another major problem with nanomedicine lies in the domain of intellectual property. Because nanotechnology is an incredibly rapidly developing area, with the potential for a lot of money to be made, everybody is patenting every single discovery they make and there are roughly 100 new patents a year on dendrimer designs alone. Between 1996-2000 there were 433 new patents on dendrimers, and between 2001-2005 there were over 1000.<sup>15</sup>

There are two arguments to this. The first being that although patents were designed to increase innovation in research because the ideas would be published and scientists could benefit from the knowledge and then expand upon it; there is a problem that if one group achieves patent dominance, it could restrict innovation. An example of this was the highly contentious case of the BRCA-1 and BRCA-2 genes, both being markers of breast cancer. However Myriad charged so much money for access to the patent that it was thought to be restricting patient care, even though the potential technology was already in use. It was just being monopolised by one company.

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<sup>15</sup> Foley and Lardner: Attorneys at law, Dendrimers and Nanotechnology: A Patent Explosion

The other argument is that the commercialising of nanotechnology is advanced by intellectual property because everyone can share ideas and it allows for companies to design around the published ideas. It also means that there is more money being made in this field of research, which provides an incentive for more research and a greater chance of an important breakthrough.

### **The Future of Nanomedicine:**

In order to effectively create new medicines, the bridge between engineers and biologists must be crossed. In the future there will be more tailored courses for nanomedicine, incorporating both the physical concepts of nanotechnology, and the biological knowledge needed to understand cellular interactions and what is needed to treat the target disease.

### **Conclusion:**

Nanotechnology is still very new. The full implications of the technology are not yet known, and the circulation of apocalyptic prophecies of the machine uprising do nothing to inspire public trust in this new field. This paper suggests that these risks must be remembered, but should not stand in the way of what could be a revolution of modern medicine. The treatments could save lives, save money for the government and lead to even more exciting breakthroughs.

None of the mentioned technologies have passed clinical trials. However treatments such as the gold nanoshells are currently being tested with positive results. The alternatives that exist all have side effects that currently seem more dangerous than the side effects of nanomedical alternatives. There are some problems with the ideas suggested, such as the monitoring systems, which over time would have problems staying within the body, and may cause an immune response. However this problem is being tackled and molecules such as poly (ethylene glycol) seem to be increasing the time that these nanoparticles can remain in the body.

Overall, this paper supports the introduction of nanotechnology, and foresees the replacement of current therapies with new, less invasive and dangerous treatments. It cannot be known if this will happen, because there are obstacles that need to be overcome in order to produce a successful drug. It should also be noted that while nanotechnology is one promising area of medical advancement in the field of oncology, there are other more targeted drugs being researched, some which are well into clinical trials, such as the drug known as “olaparib” which is being produced by Astrazeneca<sup>16</sup> as a drug that targets cancer caused by the BRCA gene by inhibiting the cancer’s DNA repair mechanism (dubbed the “Achilles’ foot” of certain cancer types)<sup>17</sup>

So while nanotechnology shows promise, other technologies cannot be forgotten in the fight against cancer. Eventually some or all of these technologies will hopefully lead to treatments with higher success rates, and maybe eventually a cure.

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<sup>16</sup> <http://clinicaltrials.gov/ct2/show/NCT00912743>

<sup>17</sup> <http://news.sky.com/skynews/Home/UK-News/Olaparib-Drug-Gives-Hope-Of-Breakthrough-Against-Cancer-As-BRCA-Mutation-Victim-Fights-Disease/Article/200906415318125>

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