

Nanotechnology and Developments in  
Tissue Reconstruction and Regeneration

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## **Abstract**

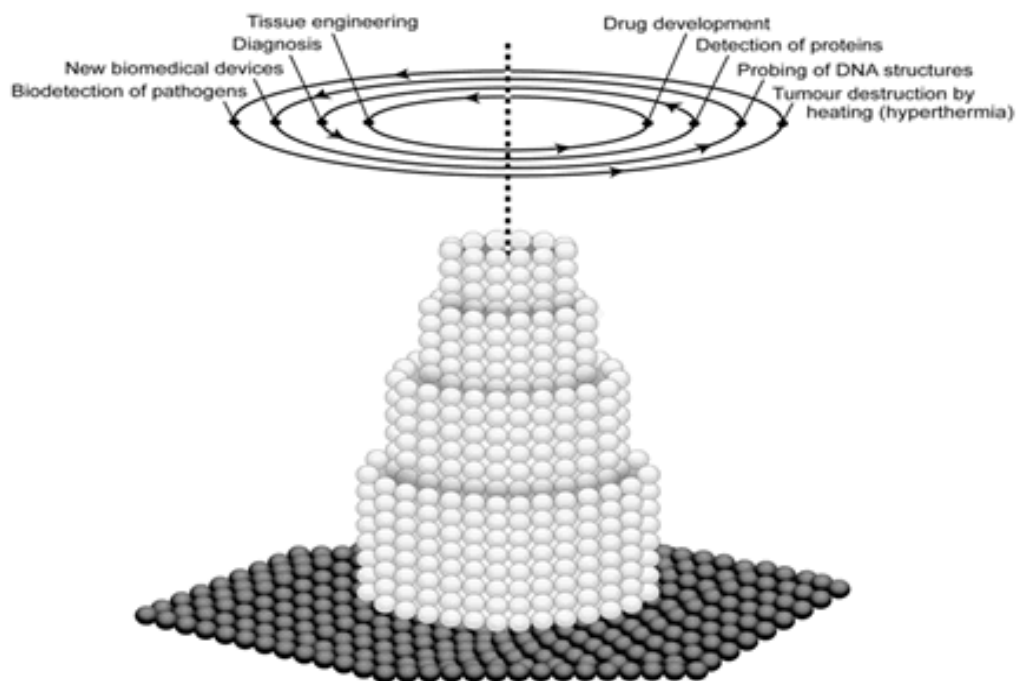
This paper considers a range of applications and developments in nanotechnology, including those affecting diagnostic medicine and treatment, but then there is a focus on tissue reconstruction and regeneration. Topics covered include the use of polymeric materials and bioactive glass to act as cytoskeletons for bone and tissue regeneration, and the use of nano-drugs to promote tissue regeneration. The commercialisation and ethical issues surrounding nanotechnology are investigated, and consideration is given to regulation of the technology and potential misuse.

## **Introduction**

'Nano' is a term derived from the Greek word 'nanos' meaning dwarf. Nanotechnology involves the very precise manipulation of materials that are of atomic and molecular size between around 0.1 nanometres and 100 nanometres (nanometres = nm,  $1\text{nm} = 1 \times 10^{-9}\text{ m}$ ), to allow the creation of new materials whose properties include being harder, stronger, lighter, and more advanced than those that were previously available (Meetoo, 2009). Nanotechnology has been used in "scanning tunnelling microscopes" and "atomic force microscopes" for over twenty years. It is being used in some everyday cosmetic products and sun-screen, and has recently been introduced to sports equipment such as tennis rackets and balls, waterproof ski jackets (nanotex), and nanodynamics golf-balls (United Nations Educational, Scientific and Cultural Organisation, [UNESCO], 2006).

The initial concept of nanotechnology came about as the result of the visionary ideas of James Clerk Maxwell in 1867 who conceived Maxwell's Demon, a tiny entity that would be able to handle individual molecules (Maxwell's Demon). However the origin tends to be attributed to a physicist called Richard Feynman, who in 1959 speculated that through miniaturization of machine tools and development of computers and information technology it would be possible to explore "the sub-microscopic world". The successful synthesis of Buckminster fullerenes or 'bucky balls' in the 1980s from 60 carbon atoms has contributed significantly to developments in nanotechnology, and these together with carbon nano-tubes which are extremely strong and flexible and with high electrical and thermal conductivity have led to many predictions for future use in electronics and car components (UNESCO, 2006). In addition, by basing research on designs already present in nature, scientists have 'snapped-up' the lotus flower's 'self-cleaning' ability and are copying the techniques used by the flower to apply them to fabrics, such as sunshades and sails, items regularly exposed to the elements and yet difficult to wash (Nanotechnology and Self Cleaning Textiles). In recent years, nanomedicine has begun to evolve the concept of miniaturization in ways to benefit the body, and today it is "a rapidly evolving, complex area of medicine where there could be massive improvements in all aspects of medicine" (Mundy, Merlin, Braunack-Mayer and Hiller, 2007). What this paper aims to discover is how different aspects of nanotechnology research have influenced developments in tissue reconstruction and regeneration.

It is known that “disease and ill health are caused largely by damage at the cellular and molecular level” (Meetoo, 2009). Scientists are building nanodevices molecule by molecule, which allows them to use the unique chemical, physical and electrical properties of materials that are found at nanoscale. This technology has the potential to revolutionise the way patients are diagnosed and treated and could “facilitate the repair, and improvement of the human body from the inside out, with far greater precision and delicacy than is currently possible” (Lupton, 2007). The following illustration (Figure 1) indicates the areas in which nanotechnology is revolutionising biomedical sciences.



**Figure 1:**

<http://www.azonano.com/Details.asp?ArticleID=1242>

It is now possible that tiny robots called nanobots which are directed by special new computers “could be designed, manufactured and introduced to the human body to perform cellular repairs at the molecular level” (Freitas, 2005). Current medical tools are “large and crude” in comparison to nanotools that could be developed in the future. A scalpel blade is around 0.2-0.4mm thick. A nanobot designed and developed to be used in the same surgery would be no more than 100nm thick, potentially 2000x smaller, which would be less invasive, and provide a quicker recovery time with theoretically less risk of infection (Allhoff, 2009). Small nanobots could also be used to manipulate individual molecules and atoms to achieve very specific cell repair. (25 ways nanotechnology is revolutionizing medicine). This could radically alter the way surgery is performed and give better outcomes for patients.

In addition, laser surgery performed at nanoscale could vaporise targeted tissues without causing damage to adjacent cells (Allhoff, 2009).

In diagnostics, new sensitive imaging techniques using quantum dots and lipid based nanoparticles as contrast agents are in the developmental phase, (Allhoff, 2009), but Combidex® nanoparticles already have conditional approval to be used with Magnetic Resonance Imaging (MRI) scanners to locate cancerous lymph nodes (Mundy, 2007). In addition, work done by Dr. Chad Mirkin to develop disease related molecules at an early stage has resulted in the 'bar code' test, detecting tiny protein traces that are associated with Alzheimer's disease (Kenwright and Pifer, 2010). The ability to achieve earlier diagnosis will allow doctors to start treatment for disease before permanent damage occurs to tissues and organs (Leary, 2010).

The National Cancer Institute (2005), as cited by Allhoff (2009), has indicated that nanotechnology products will have an enormous impact in cancer diagnosis and treatment. To help diagnosis, gold nanoparticles for example, can be attached to antibodies for a specific protein growth factor receptor found on cancer cell membranes, so that these cells can be easily identified in biopsy samples as a result of their different "light scattering and absorption spectra". Cancer research has already seen improvement in some recent chemotherapy treatments because of nanotechnology formulations. These have reduced side effects and toxicity to the patients receiving them, and clinical trials involving 'engineered nanoparticles' are now under way (McNeil, 2009).

The opportunity to treat individual cells of the human body and "eradicate disease at single-cell level" is fantastic. This is already being developed via 'smart drugs' and targeted and controlled drug therapies such as the molecular biosensors which can provide individual cell doses (Leary, 2010). Nano-capsules with feedback control could be used for diabetic patients to release insulin into the bloodstream in the correct amount, and adjusted according to blood glucose levels (Meetoo, 2009); whilst drug carrying magnetic nanoparticles are already being tested in vivo to treat bone diseases such as osteoporosis (Tran and Webster, 2009). In respiratory medicine, research has indicated that inhaled nano-sized particles of ventolin used to treat asthmatic patients could penetrate the lungs better than the micro-sized particles of current inhalers (Kenwright and Pifer, 2010). The speed of absorption of drugs is important to their success, and it is thought that reduced drug size and altered delivery mechanisms possible with nanomedicine, such as creams that are readily absorbed through the skin instead of oral medications, may help with patient compliance (Allhoff, 2009).

The ability to apply coatings to implanted medical devices of antimicrobial nanoparticles would hugely reduce the risk of infection – for example in catheters.

Already, successful nanoparticle antimicrobial coatings have been used in cochlear implants to prevent possible infection through meningitis (Mundy et al, 2007). In 2006, the first human trial for a new nano-bandage has resulted in a new "ultrafine polymer fibre" bandage which is lightweight and inexpensive, and allows oxygen to enter the wound but at the same time conforms to any wound without sticking (Nanotechnology's contribution to reconstructive surgery).

## **Discussion and Ethical Considerations**

Nanotechnology techniques for tissue regeneration and reconstruction are still at the in vitro or animal model experimental stage (Mundy et al, 2007), but Watts (2011) has found this area of research particularly interesting. Patients who have suffered severe burns over a high percentage of their body may not have sufficient skin of their own for grafting to the most damaged parts of the body, so new skin has to be grown from the patient's own skin cells. Following the discovery that nanostructures can influence the way a line of cells can develop, research has demonstrated that to help these cells multiply, they can be grown on a "polymeric material surface" and re-implanted once sufficient skin is available. Problems encountered have included "erratic development of human cells" owing to imperfections in the nanomaterials structure. However, whilst still at an early stage, a team of European scientists headed by Professor Hintz are working on a laser-based technology called EUV (Extreme Ultra-Violet) on a project called "ModPolEUV". This EUV laser has been used to create "new kinds of polymeric materials", and allows a much higher degree of precision (10-20nm) than previously (100nm). They have discovered that by using different types of polymeric materials, different types of cells for example muscle, nerve and bone can be grown, and could also be used to design new artificial implants for the future, with less risk of rejection e.g. heart implants. This could massively impact on many different surgical procedures (Nanotechnology's contribution to reconstructive surgery). New electrospun biomimetic scaffolds and stem cell technologies are currently being tested for use in wound dressing and skin tissue engineering, but it is acknowledged that at present there are still many challenges to face before in vivo applications are possible (Zhong, Zhang and Lim, 2010).

There are exciting prospects for nanotechnology developments in orthopaedic medicine for bone regeneration and reconstruction. "Bone has a vast capacity for regeneration from cells with stem cell characteristics" and it is known that there are different growth factors which stimulate bone growth, collagen synthesis and repair of fractures in vitro and in vivo (El Ghannem, 2005). Bone disease is very common. Bioactive glasses have been used for over 30 years as a bone substitute and can act as a template to "stimulate new bone growth as they dissolve in the body".

However it has been found that they cannot be sited where they are under load (Mahony and Jones, 2008). It is thought that by gaining a fuller understanding of the interaction between cells and nanostructures, it will be possible to create new nano-materials to aid cell and tissue regeneration (Yim and Leong, 2005), and in fact this is borne out by more recent research which has shown that "a new generation of advanced bio-ceramics" including "hybrid bioactive materials" can demonstrate enhanced properties for bone regeneration and repair (Arcos, Izquierdo-Barba and Vallet-Regi, 2009). The most recent of these are three-dimensional macro-porous scaffolds which have been developed for tissue engineering or as porous pieces to be implanted in situ, and owing to their combined properties it is thought likely that they will play a fundamental role in the future of bone regeneration therapy (Arcos and Vallet-Regi, 2010). If successful, these would have the potential to have a significant impact on trauma victims who have multiple complex fractures and who currently spend many months unable to fully weight bear through their limbs. One source of research as cited by Kenwright and Pifer (2010), has found that by using carbon nano-tubes as a cytoskeleton, together with the patient's own stem cells, it is possible to accelerate bone growth and healing, and so reduce periods of bed-rest to just one month for leg fractures.

Currently artificial implants for joint replacements tend to last 10-15 years and then need revision. This limits the age at which patients are able to present for initial surgery owing to complications and risks of further surgery. Current studies have already demonstrated that the functions of bone-forming cells (osteoblasts) are improved in terms of "adhesion, proliferation, synthesis of bone-related proteins, and deposition of calcium-containing minerals" on nano-structured implants made of "metals, ceramics, polymers, and composites" rather than traditional ones. This could improve bony integration which is vital for "long-term implant efficacy" (Tran and Webster, 2009). It is cited by Meeto (2009), that what is most important is the ability of the implant to mimic the mechanical properties of human bone and through nanoscale construction and engineering of joint surfaces this will be possible.

In the near future it is likely that newly developed nano-drugs can be targeted to specific bony sites to aid cartilage regeneration, as soon as there are early clinical signs of damage. "In situ regenerative medicine" will allow repair of existing cells instead of destroying diseased ones, and will programme the cells along a less dangerous cell pathway to prevent those tissues from being destroyed (Leary, 2010). Perhaps alternatively, procedures will be carried out using nanoscale laser surgery instead of conventional techniques such as arthroscopy that carries a risk of joint swelling, pain, or infection post-operatively owing to the size of instruments used. Where implant is necessary, it is possible that new nano-materials will be

sufficiently strong and versatile to prevent subsequent surgery being required, and this may enable younger people to be considered.

It is possible that small nano-chips implanted in an individual's body could monitor health and body systems and send feedback to a computer (25 ways nanotechnology is revolutionizing medicine). Perhaps more long term it will be the developments in gene regulation that will enable people who have a predisposition to particular disease or high family traits of disease to be able to be treated either with nano-drugs or injection to prevent disease from developing, or in a less severe form. Gene regulation may swap an abnormal non-functioning gene for a normal one, or regulate the degree to which the gene is turned on or off (Mundy et al, 2007).

Research is considering the possibilities of specific organ regeneration e.g. liver and kidneys. It is thought that using nano-engineered growth factors, healthy cells could be grown to replace damaged ones (Nanotech for New Organs). Obviously it remains to be seen whether cells will ultimately be regenerated in situ in the patient or whether transplantation will occur following growth of tissues in vitro. This area of nanotechnology raises lots of ethical considerations as new enhanced cells engineered to avoid particular gene strains or potential disease developments could be seen by some people as tampering with nature and a step too far. Also it has to be considered whether it is right to extend a person's natural lifespan through cell modification to prevent disease exacerbation, and how this would impact on a global scale.

Whilst treatment options will undoubtedly improve with nanomedicine, the unknowns are worrying and owing to the tiny size of synthetic nanoparticles, analysis of risk is "uniquely difficult and different". Owing to the differences in magnetic properties of nanomaterials as well as altered electrical, chemical and biological properties, safety issues may be quite different to those of other particles (McGee, 2009). Early research on animals indicates that nano-materials do accumulate in the body and may be overtaken by bacteria which could pose the risk of infiltration of the food chain (Bonsor and Strickland, 2007). Linkov, Satterstrom and Corey, (2008) have highlighted that research tends to focus on the medical applications of nanotechnology and side effects tend not to be taken into consideration during the engineering process. Any long-term effects of treatment with nanoparticles that have entered cells are obviously not yet known in terms of "adsorption, distribution, metabolism and excretion" (Mundy et al 2007), and in addition toxicity factors will need to be taken into consideration, for example, if nano-chips that are kept inside the body for a long time (Allhoff, 2009).

Funding for nanotechnology research is high, and currently it is not possible to determine the likely cost savings associated with nanomedicine when compared with conventional medical techniques. As yet, nanotechnology is not particularly high profile, but there are significant amounts of money dedicated by the Governments of different countries to developing 'nano-scale science research,' and these will obviously influence the agenda of nanomedicine projects undertaken. It is vital that alongside research, regulatory bodies are set up to oversee the type of research as well as any hazard or exposure risks from the use of nanotechnology materials. This raises its own problems on a global scale, as different cultural and political traits allow for different levels of tolerance of risk (UNESCO, 2006). In addition ethical guidelines and policies must ensure that nanotechnology cannot be used for any harmful purpose e.g. self-replicating nano-machines. The issues of justice and fairness in accessibility and availability of nano-medical techniques must be taken into consideration, both on a worldwide scale when comparing "first world against third world countries," and locally, when comparing small, rural communities with large cities (Mundy et al, 2007). UNESCO, (2006) has indicated the need for international ethical standards for nanotechnology using an anticipatory approach as new developments are occurring so quickly. Unfortunately with such a wide range of potential uses of nanotechnology it is possible that through the development of complex molecular machines, chemical and biological warfare could become a huge risk in the wrong hands, and it is vital that Governments co-operate and collaborate to ensure that this does not happen.

Already funding for new drugs and equipment is a major problem in the NHS. Cancer drugs can cost thousands of pounds a month for one patient and there are issues regarding geographical availability. It is important therefore, that as and when nanotechnology techniques and remedies are introduced, with or without cost savings compared to conventional techniques, they are available to all.

Another important consideration is whether new nanotechnologies should be regulated for use only in the scientific and medical worlds, or whether they should also be permitted in the world of sport for example? Respirocytes (artificial red blood cells) are a technology being developed by Freitas that, whilst still in the early stages, could improve survival rates from heart attacks and strokes by providing a much greater dose of oxygen to respiring tissues than red blood cells under natural circumstances. These same respirocytes could also allow someone to hold their breath for nearly four hours, so competitive swimmers potentially would be able to achieve new feats of endurance and speed, and would be placed at a huge advantage to other competitors who did not have access to them (Toth-Fejel, 2009).

Protection against infringement of privacy rights is particularly important in nanomedicine (McGee, 2009), and should be considered both on an individual basis

where nano-particle information from nano-chips implanted in the body is stored on a database, or monitored externally perhaps on the patient's own computer; and also, on a much larger scale, where information from nanotechnology devices is used in electronic health records, or on a biological database to determine whether genetic traits can effect surgical outcomes of treatment (Weiner, 2010). Where new nanotechnology surveillance systems become available using tiny webcams, regulation will be vitally important to avoid potential misuse, especially as the general public may be potentially unaware (25 ways nanotechnology is revolutionizing medicine).

## **Conclusion**

Nanotechnology is already making a positive contribution to medicine in areas of molecular imaging, diagnosis e.g. using DNA and protein nano-arrays (Mundy et al, 2007), and for specific treatments such as targeted thermotherapy to treat tumours (Meetoo, 2009). It has huge potential to influence almost every area of medicine, and pre-symptomatic diagnosis could reduce the incidence of some commonly occurring diseases for future generations with significantly reduced health costs; whilst conversely, potential increased survival rates as a result of advanced nanomedicine could exacerbate problems of an aging population, unless active and functional quality of life can be assured.

For patients who suffer serious injury, it remains to be seen whether ultimately it will be possible to reconstruct or regenerate sufficient bone and/or skin in a particular area of the body and successfully reattach muscles with intact nerves and blood supply to allow normal function. The cost implications of this would be huge, and from a commercial point of view, it may be unviable in contrast to conventional medicine. However, from a medical science perspective, it seems only a matter of time before different aspects of nanotechnology can be brought together to truly rebuild the human body. It will be up to the Governments' of particular countries to decide whether to continue to fund such innovative research, especially in light of cuts in funding as part of the aim to reduce national deficits.

The ability to target particular types of cell and administer individual cell doses via nano-engineered drugs or via precise microscopic and intracellular surgery without causing damage to surrounding cells will be hugely beneficial, and further research and time will determine whether safety and toxicity factors for these new drugs and techniques need to be addressed any more than those of conventional medicine. The potential cost savings of individual nanotechnology techniques and products can only be brought to a global market through ongoing research, and from these, the technological and practical breakthroughs for the future of which it would be wonderful to be a part.

Commercialisation of nanotechnology and the products developed in the future could be driven by influential drug companies, as they will be looking to develop nano-

drugs that provide cost effective treatment for many people rather than hugely expensive 'miracle cures' for a few. However, without innovative developments in disease diagnosis, screening, imaging and health monitoring by other research groups, the potential benefits of nano-drugs might not be fully recognised, and it is therefore important that all aspects of research and development are adequately funded and supported.

## **References**

### **Journals**

Freitas R.A. Jr. (2005) What is medicine? *Journal of nanomedicine*, vol. 1, issue 1, pgs 2-9

Kenwright K. and Pifer L.W., (2010) Nanotechnology: Nanomedicine. *Clinical Laboratory Science* vol. 23 issue 2 pgs 112-118

Meetoo D. (2009) Nanotechnology: the revolution of the big future with the tiny medicine. *British Journal of Nursing*, vol. 18, no. 19 pgs 1201-1206

United Nations Educational, Scientific, and Cultural Organization (UNESCO, 2006) *The Ethics and Politics of Nanotechnology*, Paris, France: UNESCO

Watts E. (2011) Medlink Student - Pathology Lectures

### **Websites**

Allhoff F. (2009)

The Coming Era of Nanomedicine

[files.allhoff.org/research/Coming\\_Era\\_Nanomedicine.pdf](http://files.allhoff.org/research/Coming_Era_Nanomedicine.pdf)

Arcos D, Izquierdo-Barba I, Vallet-Regi M (2009)

Promising trends of bioceramics in the biomaterials field

[www.ncbi.nlm.nih.gov/pubmed/18987955](http://www.ncbi.nlm.nih.gov/pubmed/18987955)

Arcos D, Vallet-Regi M, (2010)

Sol-gel silica-based biomaterials and bone tissue regeneration

[www.ncbi.nlm.nih.gov/pubmed/20152946](http://www.ncbi.nlm.nih.gov/pubmed/20152946)

Bonsor and Strickland (2007)

[www.howstuffworks.com/nanotechnology](http://www.howstuffworks.com/nanotechnology)

El Ghannem A, (2005)

Bone reconstruction: from bioceramics to tissue engineering

[www.ncbi.nlm.nih.gov/pubmed/16293032](http://www.ncbi.nlm.nih.gov/pubmed/16293032)

Leary JF. (2010)

Nanotechnology: what is it and why is small so big?

<http://www.ncbi.nlm.nih.gov/pubmed/20856270>

- Linkov I., Satterstrom F.K., and Corey L.M. (2008)  
Nanotoxicology and nanomedicine: making hard decisions  
[www.nanomedjournal.com/article/S1549-9634\(08\)00002-6/abstract](http://www.nanomedjournal.com/article/S1549-9634(08)00002-6/abstract)
- Lupton, M. (2007)  
Nanotechnology – salvation or damnation for humans? *Journal of Medicine and Law*, vol. 26, issue 2 pgs 349-362  
[www.ncbi.nlm.nih.gov/pubmed/17639856](http://www.ncbi.nlm.nih.gov/pubmed/17639856)
- Mahony O, Jones J.R. (2008)  
Porous bioactive nanostructured scaffolds for bone regeneration: a sol-gel solution  
[www.ncbi.nlm.nih.gov/pubmed/18373428](http://www.ncbi.nlm.nih.gov/pubmed/18373428)
- McGee E. (2009)  
Nanomedicine: Ethical Concerns beyond Diagnostics, Drugs, and Techniques. *The American Journal of Bioethics*. vol. 9, issue 10, pgs 14-15  
[www.observatoribioetica.com/indices/AJB/AJBoct09.pdf](http://www.observatoribioetica.com/indices/AJB/AJBoct09.pdf)
- McNeil S.E. (2009)  
Nanoparticle therapeutics: a personal perspective. *Wiley inter disciplinary review* vol. 1, issue 3 pgs 264-271  
<http://onlinelibrary.wiley.com/doi/10.1002/wnan.6/abstract>
- Mundy L., Merlin T., Braunack-Mayer A. and Hiller J. (2007)  
Nanotechnology; emerging technology bulletin  
[www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=32006001414](http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=32006001414)
- Toth-Fejel T. (2009)  
Nanotechnology will change more than just one thing. *The American Journal of Bioethics*, vol. 9, issue 10, pgs 12-19  
[www.observatoribioetica.com/indices/AJB/AJBoct09.pdf](http://www.observatoribioetica.com/indices/AJB/AJBoct09.pdf)
- Tran N. and Webster T. (2009)  
Nanotechnology for bone materials  
[www.ncbi.nlm.nih.gov/pubmed/20049801](http://www.ncbi.nlm.nih.gov/pubmed/20049801)
- Weiner B (2010)  
[www.azom.com/news.asp?newsID=20393](http://www.azom.com/news.asp?newsID=20393)

Yim E.K. and Leong K.W. (2005)  
Significance of synthetic nanostructures in dictating cellular response  
[www.ncbi.nlm.nih.gov/pubmed/17292053](http://www.ncbi.nlm.nih.gov/pubmed/17292053)

Zhong S.P., Zhang Y.Z., and Lim C.T. (2010)  
Tissue Scaffolds for skin wound healing and dermal reconstruction  
[www.ncbi.nlm.nih.gov/pubmed/20607703](http://www.ncbi.nlm.nih.gov/pubmed/20607703)

25 ways nanotechnology is revolutionizing medicine (Jan 2010)  
[mritechnicianschools.net/2010/25-ways-nanotechnology-is-revolutionalizing-medicine/](http://mritechnicianschools.net/2010/25-ways-nanotechnology-is-revolutionalizing-medicine/)

Maxwell's Demon (n.d.)  
[www.auburn.edu/~smith01/notes/maxdem.htm](http://www.auburn.edu/~smith01/notes/maxdem.htm)

Nanotech for New Organs (n.d.)  
[www.nanotechnologist.com/new-organs/index.html](http://www.nanotechnologist.com/new-organs/index.html)

Nanotechnology's contribution to reconstructive surgery  
[www.nanowerk.com/news/newsid=19741.php](http://www.nanowerk.com/news/newsid=19741.php)

Nanotechnology and Medicine  
[www.nanotechproject.org/inventories/medicine/](http://www.nanotechproject.org/inventories/medicine/)

Nanotechnology Self Cleaning Effects for Textiles  
[www.jobwerx.com/news/basf-biz-949032-422.html](http://www.jobwerx.com/news/basf-biz-949032-422.html)