# Nanotechnology in Good Health?*

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The business environment for large pharmaceutical companies is changing. Profits from blockbuster drugs are under threat due to expiration of patents. Healthcare will change because of the ever increasing cost to develop drugs. The only way forward, to become more efficient in cost and patient care, will be through nanotechnology.

For those not familiar with nanometres (nm), they are one millionth of a millimetre. To appreciate this more easily, a human hair is about 80,000 nanometres in diameter, red blood cells are about 5,000 nm across, the AIDS virus is approximately 100 nm long, and DNA is less than 3 nm. At the nano-scale properties change, and the reason for this can be understood if one considers a cube of just about any substance, which would have one in ten million of the atoms on the surface. However, for a one nanometre cube, 80% of the atoms are on the surface. This increased surface area can be beneficial for many technologies and products. For several years now, car exhaust catalysts have relied on nanotechnology and the increased surface area it provides to breakdown exhaust fumes.

A project on emerging nanotechnologies at the Woodrow Wilson International Centre for Scholars to date has catalogued over 500 manufacturer-identified, nanotechnology-based products.[1] These include numerous sun-screen products in which the nanoparticles of titanium dioxide, $TiO_2$, let the *good* ultraviolet light through but reflect the *bad* UV. In addition, there are an increasing number of products—ranging from socks and towels to refrigerators and food storage containers—that incorporate silver nanoparticles, which provide antimicrobial properties. Many wound dressings now contain silver nanoparticles to aid faster recovery. The earliest applications for nanotechnology products have been in sporting goods,[2] where the margins are high, *e.g*. Federer's tennis racket, lighter weight materials in Formula One racing cars, and Floyd Landis's cycle frame. Once established in those markets, the technology moves down to commodity products, which is certainly what is happening with most automotive companies.


For consumer products that provide healthcare, we are seeing many new types of toothpaste on the market which are based on nanotechnology. Guaber in Italy make BlanX®, containing NANOREPAIR™, which is treated nanoparticulate hydroxyapatite for filling the minute cracks that occur in the enamel of teeth. A similar system is available for hair damage repair, which is called TANAGRA, and contains *nano-molecular* keratin to block cracked or rough hair. L'Oreal has the largest number of patents relating to nanotechnology in health and personal care,[3] many of which are for anti-ageing products. Their significant R&D expenditure in nano-capsule technology is directed at delivering agents such as vitamin A and retinol into the skin.

However, the most promise for nanotechnology will come from *nanomedicine*, which has been described as the application of nanotechnology to achieve breakthroughs in healthcare.[4] Nanomedicine promises to impact all stages of healthcare:

- preventative medicine
- diagnosis
- therapy
- follow-up care

Proponents of nanomedicine hold that it will lead to earlier detection of diseases and novel therapies that will minimize discomfort for the patient, and hence provide cost savings all around. The European Strategic Research Agenda for nanomedicine[4] has set priorities based on a number of parameters, namely: mortality rate, level of suffering, burden on society, prevalence of the disease, and the ability of nanotechnology to diagnose and overcome illnesses.

The strategy is to attack the diseases that are the greatest burden on society first:

- cardiovascular diseases
- cancer
- musculoskeletal disorders
- neurodegenerative diseases and psychiatric conditions
- diabetes
- bacterial and viral infections.

According to the World Health Organization,[5] cardiovascular diseases are the most frequent cause of death in the EU. However, efforts to reduce heart-related problems by encouraging more exercise and a reduction in cholesterol levels are paying off, and cancer instead may soon become the leading cause of death. In the US, nanotechnology solutions for cancer therapy are receiving high priority. A *Cancer Nanotechnology Plan*[6] is being spearheaded by the National Cancer Institute, which acknowledges that *nanotechnology offers the unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the early stages of the cancer process.*

It is worth listing part of the vision statement for the Cancer Nanotechnology Plan, which says that nanotechnology will be the enabling technology for:

- early imaging agents and diagnostics that will allow clinicians to detect cancer at its earliest, most easily treatable, pre-symptomatic stage
- systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation
- multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high concentrations, with physiologically appropriate timing, directly to cancer cells and those tissues in the micro-environment that play a critical role in the growth and metastasis of cancer
- agents capable of monitoring predictive molecular changes and preventing precancerous cells from becoming malignant
- surveillance systems that will detect mutations that may trigger the cancer process and genetic markers that indicate a predisposition for cancer
- novel methods for managing the symptoms of cancer that adversely impact quality of life
- research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance.

Nanomedicine can be divided into four main areas:

- drug delivery
- molecular diagnostics
- tissue engineering
- cell/gene therapy

## Drug Delivery

In addition to all the proposed new work discussed above, the challenge for the traditional pharmaceutical companies is to deliver the right therapeutic to the right target with no (or minimal) side effects, and at reduced cost. Drug delivery using nanostructures offers considerable potential to accomplish this. Some early successes have come from the Elan Corporation, a neuroscience-based biotechnology company headquartered in Dublin, Ireland. They have developed proprietary NanoCrystal technology for active pharmaceuticals that have poor water solubility. This technology reduces the particle size and increases the surface area of drugs leading to an increased dissolution rate. The nanoparticles are processed into finished dosage forms for all methods of administration. There have been four commercial approvals for products that have incorporated this type of technology, *viz*.:

- *Rapamune*, Wyeth's immunosuppressant, now in tablet form; previously it was available as a refrigerated product in packets or in bottles.
- *Emend*, which was developed as a new chemical entity by Merck for cancer treatment.
- *TriCor*, a reformulated drug for lowering cholesterol from Abbott; previously it had to be taken with a meal.
- *Megace ES* is an appetite enhancer for AIDS sufferers from Par Pharmaceuticals who have licensed the Megace name from Bristol-Myers Squibb. NanoCrystal technology improves the rate of dissolution and bioavailability of the original unpalatable oral suspension.

In the US, the company Esprit Pharma markets *Estrasorb* (from Novavax). This is an emulsion containing nanoparticles that is rubbed onto the legs to reduce hot flushes. There are two other cancer therapy drugs that are now nanotechnology-based: *Abraxane* for fighting metastatic breast cancer (Abraxis BioScience and AstraZeneca) and *Doxil* for ovarian cancer (Ortho Biotech).

A NanoMarkets report[7] suggests that \$US 65 billion p.a. in drug revenues are accounted for by active agents with low bio-availability, which can lead to inefficient treatment, higher cost and risk of toxic side effects - hence the drive to develop reformulations based on nanotechnology. The report estimates that nano-enabled drug delivery systems will reach \$US 1.7 billion in 2009.

For cancer therapy, the goal is to target cancerous cells while leaving healthy cells intact. With nanotechnology, it is possible to specifically target the cancerous cells and then activate the nano-structures to kill just those cells. Naomi Halas and Jennifer West[8] are working on gold nanoshells that can be tailored to absorb near infrared light. This passes harmlessly through soft tissue but when nanoshells are activated under near infrared light, enough heat is generated to burst the walls of cancerous cells.[8] This breakthrough has led to the set up of spin-off company Nanospectra Biosciences, which is to begin trials with the nanospheres in humans.

## Molecular Diagnostics

As indicated earlier, biological structures exist at the nano-scale, and nanomaterials are being used for both *in vivo* and *in vitro* biomedical research, especially for diagnostic devices. Some technologies are now mimicking the effectiveness of *sniffer dogs* at airports, which are able to rapidly detect minute amounts of drugs or explosives very quickly. Such sensitivity has recently been reported[9] from the University of Manchester where gas sensors that use graphene to detect single gas molecules are being developed. The promise for molecular diagnosis is that diseases will, in the future, be easily and quickly detectable before they gain a foothold on the body, resulting in less severe and expensive therapy.

Hand-held *lab-on-a-chip* devices are already being used in hospitals to detect whether someone is having a heart attack. A similar development is being used to distinguish among several different narcotics in the bloodstream.

An area that has seen huge growth in the last decade is medical imaging. Here, nanotechnology applications are beginning to appear for both imaging tools and marker and contrast agents. It is expected, in the foreseeable future, that nano-imaging will lead to the detection of single cells in very complicated environments.

In 2005, the molecular diagnostics market was about $US 5.5 billion, and the nano-diagnostics share was about $US 1 billion. It is estimated that by 2015, the nano-diagnostics market will be worth $US 9.5 billion and will predominate the molecular diagnostics market.[10]

## Tissue Engineering

Tissue engineering uses developments from materials engineering and the life sciences to provide biological substitutes that will reproduce or repair damaged tissue. Tissue engineering stimulates cell proliferation using nanomaterial scaffolds, which are porous or solid. It is expected that in the future, tissue engineering will enable the replacement of artificial implants and organ transplants.

Nanotechnology is already contributing to commercially available products. *NanOss* and *Vitoss* are basically fillers for damaged bone. *NanOss* (from Angstrom Medica Inc. in the US) was the first nanotechnology medical device to receive approval from the US Food and Drug Administration. It is an innovative structural biomaterial, based on nanocrystalline calcium phosphate technology, that is highly osteoconductive and remodels over time into human bone. The material has applications in sports medicine and trauma, spine, and general orthopaedics markets. *Vitoss* (from Orthovita) also is based on calcium phosphate. It comes in blocks that can be shaped with a scalpel and gently tamped into place, or in granules that can be packed into irregularly shaped voids in the defect site. A third product, *TiMesh*, (from GP Surgical) is described as a soft-tissue reinforcement implant for hernia repair and is based on titanised polypropylene.

The market described as tissue engineering[10] was worth $US 6.9 billion in 2005 and is predicted to rise to $US 23.2 billion in 2015.

## Cell/Gene Therapy

This type of therapy repairs or replaces damaged tissue by using cells from the patient or a donor that have been multiplied and sometimes altered outside the body. A good example of this is stem cells, which can be grown and transformed into specialized cells, such as nerves and muscles, through cell culture.

SiBiono Gene Tech (based in China) was the first company to commercialize gene therapy. Its product *Gendicine* makes use of the fact that over 50% of tumours have a dysfunctional gene that makes protein p53 a cellular anti-cancer agent. Effectively, *Gendicine* works by inserting the p53 gene into a virus that is then injected into patients. The gene is naturally present in healthy cells but is *turned off* or mutated in many cancer patients. When reinserted into tumour cells by the virus, it causes them to self destruct. *Gendicine* is finding success among sufferers of head and neck squamous cell carcinoma. The only other commercially available gene therapy is from Shanghai-based Sunway Biotech, which has a virus that kills tumours. The product, called *Oncorine*, is a genetically modified virus that selectively replicates inside tumour cells with dysfunctional p53 genes.

Nanomedicine is moving forward at a rapid pace, and we are only just seeing the tip of the iceberg. The best is yet to come.

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