SOME CLINICAL APPLICATIONS OF NANOTECHNOLOGY

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ABSTRACT

Nanomedicine can be succinctly defined as the application of nanotechnologies in a healthcare setting. Nanomedicine ascends from the integration of different sciences; physics, chemistry, biology, materials science, engineering, using the nanometer scale. This leads to scientists with different backgrounds, and diversified technical and intellectual skills, trying to address medical problems using nanotechnology. The task of nanomedicine is to integrate the knowledge of physicists, chemists and biologists to reach an ideal answer. Presently, nanomedicines are being explored for the management of various disease conditions which includes fungal infections, asthma and emphysema, ovarian and breast cancer, menopausal symptoms, chronic pain, kidney disease, multiple sclerosis. Nanotechnology is creating an insurrection, a paradigm shift in the manner we diagnose and treat disease. This treatise and current research concentrates on specific fields such as Nanodiagnostics, Molecular imaging, Dental Care, Orthopedics, Cardiac therapy and newly targeted drug-delivery systems. Nanomedicine offers hope for treatment of spinal cord injuries, diabetes, heart disease, Parkinson's disease and cancer.

Keywords: *Nanotechnology; Nanomedicine; Nanodiagnostic; Molecular imaging; Dental Care; Orthopedics; Cardiac Therapy; Drug delivery.*

INTRODUCTION

Nanotechnology has several definitions but universally it is the use and application of materials with sizes in the nanometre range. Just as a millimetre is one-thousandth of a metre, a nanometre is one-millionth of a millimetre. In more comprehensible terms, a strand of human hair is around 80,000 nanometres in diameter and the rising science and industry of nanotechnology exploits materials below 1,000 nanometres. Figure 1 shows the size comparison of nanoparticles and some biological systems.

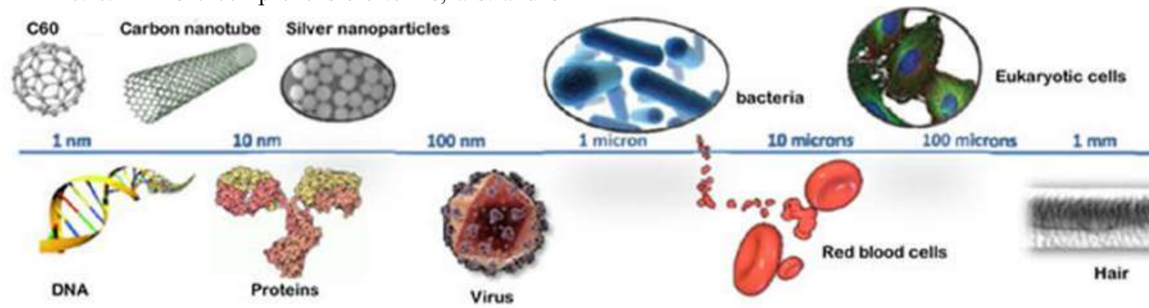

Figure 1. Size comparison: nanoparticles and biological systems

Therefore, Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter) (Badve *et al.,* 2012).

Figure 2 shows the different structures of nanomedicines and their approximate sizes. For comparison the sizes of biological nanostructures are show at the top of the figure.

Presently, this multidisciplinary scientific meadow called nanotechnology is experiencing rapid development (Cheng *et al.,* 2006).

Global Market for Nanotechnology Products is very promising. The total market for nanobiotechnology products was $19.3 billion in 2010 and is growing at a compound annual growth rate (CAGR) of 9% to reach a forecast market size of $29.7 billion by 2015. Medical applications, including drug delivery and microbicides, dominate today's market, with sales of $19.1 billion in 2010 (Figure 3). This market segment is growing at a compound annual growth rate (CAGR) of 8.7%, and is forecast to reach sales of $29 billion by 2015 (BCC). Presently, more and more consumer products are branded worldwide as "nano".

The origin of nanotechnology can be drawn from the promise of revolutionary improvements through communications, genomics, robotics and medicine. A comprehensive list of the possible applications of nanotechnology is too enormous and diverse to debate in detail, but without reservation, one of the utmost values of nanotechnology will be in the development of novel and effective medical treatments (Yoshikawa *et al.,* 2006). Figure 4 shows the many nanomedines that are already in routine clinical use.

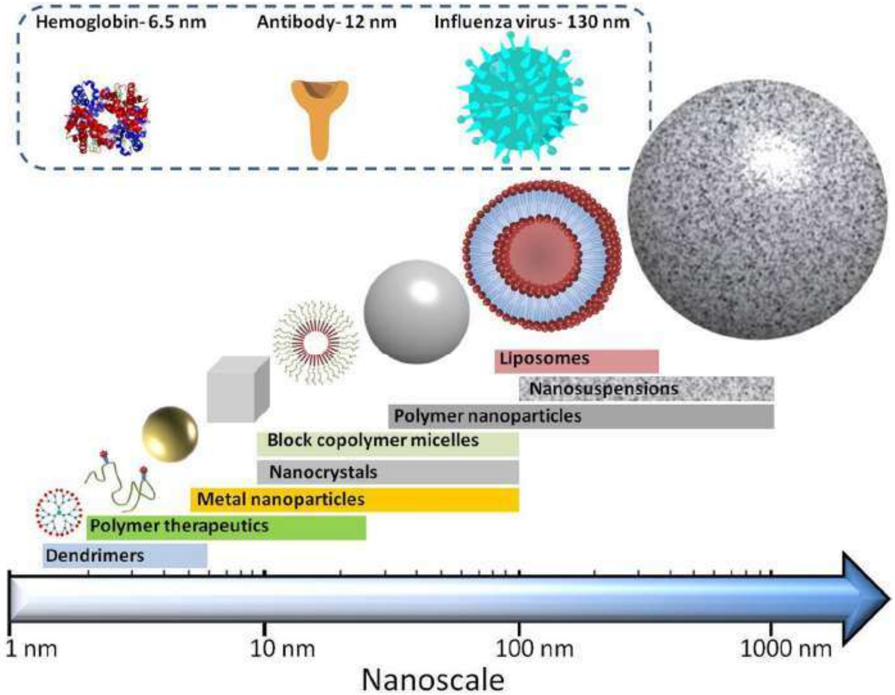

Figure 2: Structures of nanomedicines and their approximate sizes.

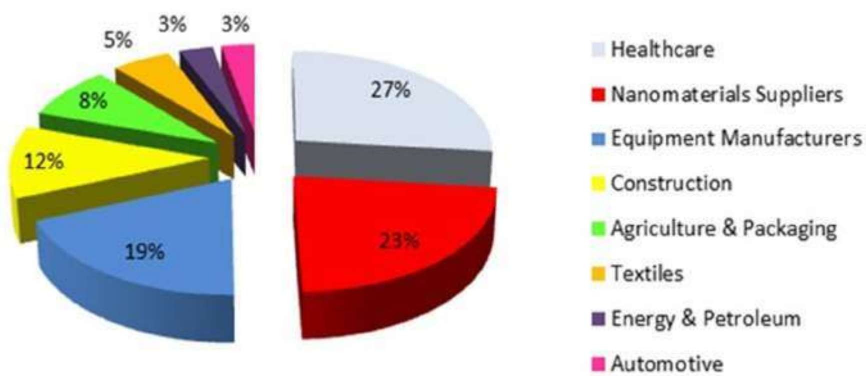

Figure 3: Market share of nanotechnology products

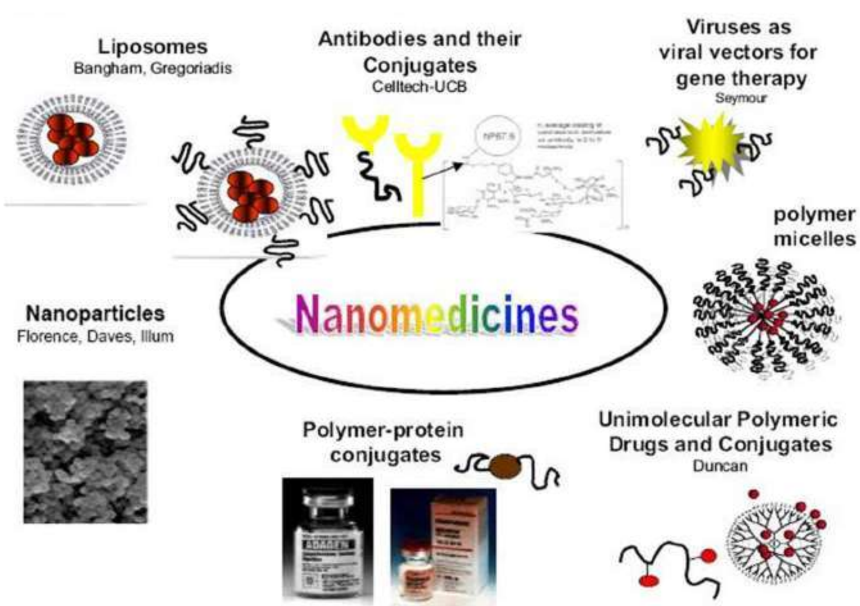

Figure 4: Some Nanomedicines already in routine clinical use.

This review concentrates on the potentials of nanotechnology in medicine otherwise known as nanomedicine.

The History of Nanotechnologies

The theoretical foundation of nanotechnology was first laid out in 1959 by Richard Feynman in his lecture, 'There's plenty of room at the bottom'. Feynman reconnoitered the possibility of influencing material at the scale of separate atoms and molecules, visualization of the entire Encyclopedia Britannica transcribed on the head of a pin and anticipating the increasing ability to study and control matter at the nanoscale. The term 'nanotechnology' was first used in 1974, when a researcher at the University of Tokyo by name Norio Taniguchi, used it to refer to the capability of engineering materials accurately at the nanometer level. The prime driving force for miniaturization then came from the electronics industry, which aimed to change tools to create reduced (and therefore faster and more complex) electronic devices on silicon chips. Additionally, at IBM in USA, a method called electron beam lithography was used to produce nanostructures and devices as tiny as 40 to 70 nm in the early 70s.

APPLICATIONS OF NANOTECHNOLOGY

1. Molecular diagnostics

Due to the minuscule dimensions, most of the applications of nano-biotechnology in molecular diagnostics are classified broadly under biochips/microarrays but are best termed nanochips and nanoarrays. Biochips constructed with micro-electromechanical systems are on a micron scale and are related to micro-manipulation, although nanotechnology-based chips are on a nanoscale and are related to nano-manipulation (Hutcheson, 2004). The chemical reformation and comprehensive amplification of the nucleic acid samples are achieved by polymerase chain reaction (PCR), which introduces artifacts instigated by the favored amplification of certain sequences. Alternative label-free methods such as surface plasmon resonance (SPR) and quartz crystal microbalance (QCM), are said to rely on mass detection. This shows that Nanotechnologies also offer label-free detection. Hence, Nanotechnology is being applied to conquer some of the precincts of biochip technology (Kubik *et al.,* 2005).

A very interesting aspect is the "lab-on-a-chip" technology otherwise called "microfluidics". Biological examinations measuring the existence or activity of selected substances become faster, more sensitive, and more flexible when definite nanoscale particles are put to drudgery such as tags or labels. Magnetic nanoparticles that are bound to a suitable antibody, can be used to label specific molecules, structures and micro-organisms (Basavaraj, 2012). Magnetic immunoassay practices have been developed, here, the magnetic field created by the magnetically labelled targets is detected unswervingly with a sensitive magnetometer. Gold nanoparticles labelled with short segments of DNA can be used for the elucidation of the genetic sequence in a sample. Many-hued optical codings for biological assays have been accomplished by embedding different-sized quantum dots QDs (nanocrystals of cadmium selenide) into polymeric microbeads. This spectral coding technology is projected to open novel opportunities for medical diagnostics (Jain, 2005).

Nanotechnology on a chip is a novel paradigm for complete chemical analytic systems. The ability to make chemical and biological information inexpensive and accessible is anticipated to fundamentally revolutionalise the health care sector, food safety organizations and law enforcement agencies. Lab-on-a-chip technology encompasses micro-total analytic systems that are differentiated from simple biosensors due to the fact that they conduct a complete analysis. Here, a raw mixture of chemicals go in and answers come out.

2. Molecular imaging

Molecular imaging techniques have had a foremost effect in medicine over the past 15 years (Kateb *et al.,* 2011). The effort in developing techniques such as functional magnetic resonance imaging is to improve spatial resolution and contrast agents. Nanotechnology has transformed the field of medicine, because it offers novel opportunities for sensing clinically relevant markers, molecular disease imaging, and tools for therapeutic intervention (Lin and Datar, 2006). Nanotechnologies gives the possibility of intracellular imaging through the addition of quantum dots (QDs) or chromophoric dyes to selected molecules as in proteins, or by the integration of naturally occurring fluorescent proteins that, with optical techniques such as confocal microscopy and correlation imaging, allow intracellular biochemical processes to be investigated unswervingly (Guccione *et al.,* 2004).

QDs are more appealing as in vivo and in vitro fluorophores in a variety of biological investigations in which traditional fluorescent labels based on organic molecules fall short of providing long-term stability and simultaneous detection of multiple signals (Medintz *et al.,* 2005). QDs have also been successfully used as new fluorescent tags in many biological and biomedical fields and show definite promise as a new tool in biomedical studies, clinical diagnostics, drug delivery, and photodynamic therapy. Nanotechnology has also been identified as a field of great promise to detect and diagnose cancer. For instance, semiconductor QDs can allow the detection of tens to hundreds of cancer biomarkers in blood assays, on cancer tissue biopsies, or as contrast agents for medical imaging (Smith *et al.,* 2006).

3. Dental care

Nanotechnology has medical applications in the field of dentistry refered to as nanodentistry which makes it possible to maintain near-perfect oral health through the use of nanomaterials (West and Halas, 2000), biotechnology Slavkin, 1999), and nanorobotics. Through this, it has been possible to provide high-quality dental care to millions of the world's population who currently receive no significant dental care (Ure and Haris, 2003). In the near future it should be possible through nanodentistry to induce local anaesthesia. A colloidal suspension containing millions of active analgesic dental nanorobotic particles could be instilled on the patient's gingivae. These nanorobots, after contacting the surface of the crown or mucosa, reach the dentin by migrating into the gingival sulcus and pass painlessly to the target site. On reaching the dentin, the nanorobots enter dentinal tubule holes that are 1 to 4 Am in diameter (Goracci and Mori, 1995) and proceed towards the pulp, guided by a combination of chemical gradients, temperature differentials, and even positional navigation, all under the control of the onboard nano computer as directed by the dentist.

Nanodental techniques for major tooth restoration are also evolving (Figure 5). Orthodontic nanorobots directly manipulate the periodontal tissues (gingivae, periodontal ligament, cementum, and alveolar bone), allowing rapid and painless tooth straightening, rotating, and vertical repositioning within minutes. Reconstructive dental nanorobots could selectively and precisely occlude specific tubules within minutes, offering patients a quick and permanent cure. Nanodentistry is also playing a vital role in natural tooth maintenance Shellhart and Oesterle (1999). The appearance and durability of teeth are improved by replacing upper enamel layers with covalently bonded artificial materials such as sapphire or diamond, which have 20 to 100 times the hardness and strength of natural enamel. A subocclusal-dwelling nanorobotic dentifrice delivered by mouthwash or toothpaste could patrol all supragingival and subgingival surfaces at least once a day, metabolizing trapped organic matter into harmless and odorless vapors and performing continuous calculus debridement Freitas, 2000).

4. Orthopedic applications

An ageing population and an increasing occurrence of sports-related injuries have made musculoskeletal disorders one of the major health concerns of all times. Current treatment modalities include orthopedic implants used for internal fixation of fractured bones, but these are limited by the large number of implant failures. In addition, these engineered implants are stiffer than those of cortical bones, and removal of the implants require a second operation. Besides, the polymers used, suffer from the drawbacks of loss of mechanical strength within a time interval and development of a sterile sinus at the site of implantation. Biomaterials proposed as ideal scaffolds for cell growth should be biocompatible, osteoinductive, osteoconductive, integrative, porous, and mechanically compatible with native bone to fulfill their desired roles as bone implants and substitutes. Current treatment have some but not all of these properties. This has prompted orthopedic surgeons and scientists to look for viable alternatives. Nanotechnology is currently providing nanomaterials with higher mechanical strength, enhanced bioactivity, and restorability in improving the quality of life of patients who suffer from debilitating bone fractures.

Nanostructured materials with sizes 1 to 100 nm are acting as new and effective constituents of bone materials, because bone is also made up of nanosized organic and mineral phases. Several studies have reported improved osseo-integration on nanostructure surfaces created from a wide range of chemistries including ceramics, metals, polymers, and composites. For instance, studies show that alumina nanometer fibers significantly stimulate osteoblast responses such as adhesion, alkaline phosphatase activity, and calcium deposition, when compared with conventional grain size alumina (Webstar *et al.,* 2004).

Nanomaterials, nanopolymers, carbon nanofibers, nanotubes, and nanocomposites of ceramics are also leading to more efficient deposition of calcium-containing minerals on the implants. Figure 6 shows the potential applications of nanomedicine in orthopedic medicine

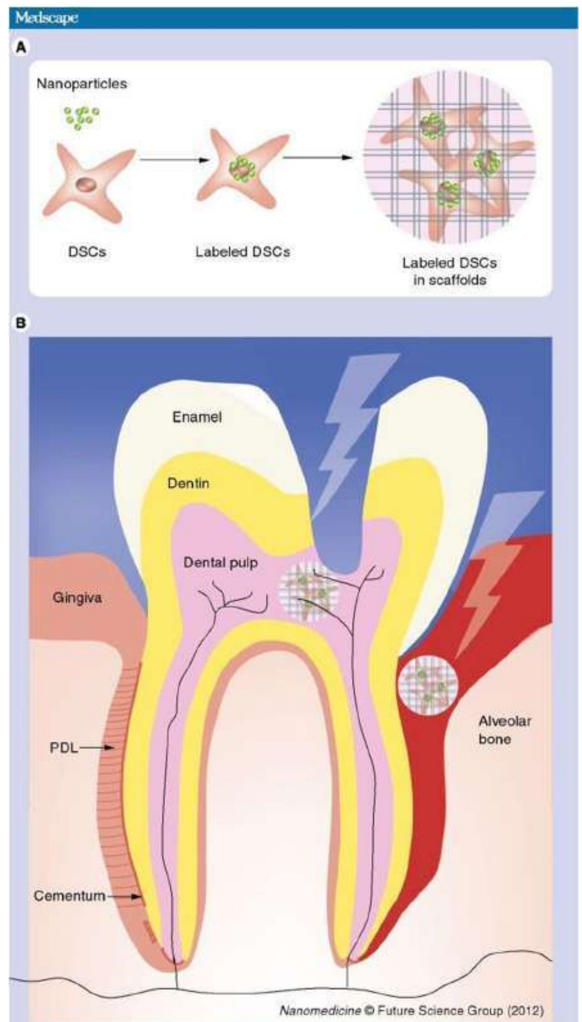

Figure 5: Nanotechnology in regenerative dentistry. ***(A)*** *DSCs can be labeled with nanoparticles before placing them into biomimetic scaffolds.* ***(B)*** *Afterwards, those scaffolds that contain labeled DSCs could be transplanted to repair damaged dental tissues. Tooth crown, pulp and periodontium are the most commonly affected dental tissues. DSC: Dental stem cell; PDL: Periodontal ligament.*

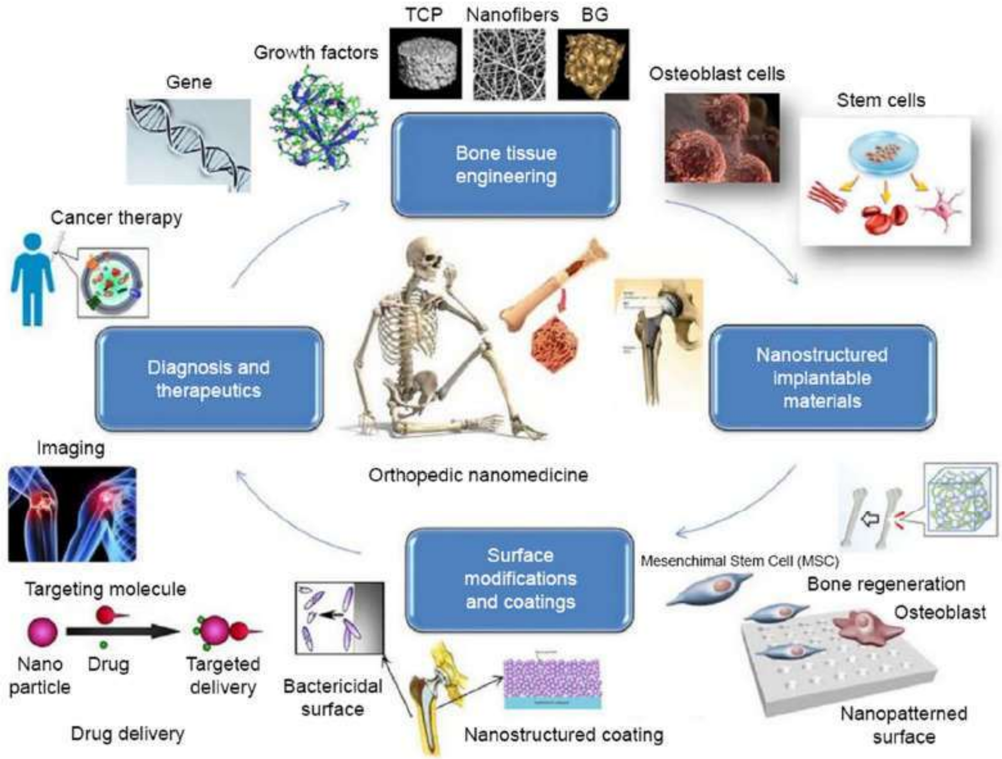

Figure 6: Scheme showing potential applications of nanomedicine in orthopedic medicine

5. Cardiac therapy

Cardiac diseases are a major cause of disability, morbidity and mortality. Many people are dying of various cardiac problems including atherosclerosis, myocardial infarction, arrhythmias, ischemic heart disease, and restenosis (Kong and Goldschmidt-Clermont, 2005). Oral and systemic administration of drugs, though effective, does not provide appropriate therapeutic drug levels in the target arteries for sufficient periods of time. Moreover, biomedical engineers have already succeeded in developing microscale instruments to open blocked arteries and to treat other cardiovascular diseases. However, these tools are bulky, infection prone, and subject to other disorders. Currently nanotechnology offers a broad platform in the field of cardiovascular science by offering tools to explore the frontiers of cardiac science at the cellular level. Nanotechnology based tools are being effectively used to treat cardiovascular diseases (Figures 7). These tools are used in the areas of diagnosis, imaging, and tissue engineering (Wickline, 2006). Miniaturized nanoscale sensors like QDs, nanocrystals, and nanobarcodes can sense and monitor biological signals such as the release of proteins or antibodies in response to cardiac or inflammatory events (Guccione *et al.,* 2004). Nanotechnology is helping in revealing the mechanisms involved in various cardiac diseases. It also helps in designing atomic-scale machines by imitating or incorporating biological systems at the molecular level. The use of these newly designed nanomachines have a paradigm-shifting impact in the treatment of these dreaded cardiovascular diseases. These machines have three key elements meant for sensing, decision making, and carrying out the intended purpose.

Restenosis, the obstruction of an artery after interventional procedures such as balloon angioplasty, remains a major problem, in that 30% to 50% of patients develop reocclusion, with 20% requiring additional intervention (Brigger *et al.,* 2005). Although different therapeutic strategies have been investigated for the inhibition of restenosis, the main drug therapeutic approach is targeted towards inhibiting the proliferation and migration of smooth muscle cells (Hamon *et al.,* 1998). Systemic administration of therapeutic agents has been ineffective in preventing restenosis. The main reason for the failure of drugs in clinical trials is the inefficacy of such an approach in providing therapeutic drug levels in the target tissue for a sustained period of time. Therefore, researchers have a great hope that nanotechnology-based localized drug therapy using sustained-release drug delivery systems could be more effective, because it can provide higher and prolonged drug levels in the target tissues without causing systemic toxicity (Panyam and Labhasetwar, 2003). Nanotechnology could also have an impact in the diagnosis and treatment of unstable plaques and in the management of other cardiovascular problems like calcification of valves. Thus, nanotechnology could be an effective treatment modality to achieve localized and sustained arterial and cardiac drug therapy for the prevention of cardiovascular diseases.

6. Drug delivery

From nanotechnology there is only one step to nano-medicine, which may be defined as the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nano-structures (Moghimi *et al.,* 2005).

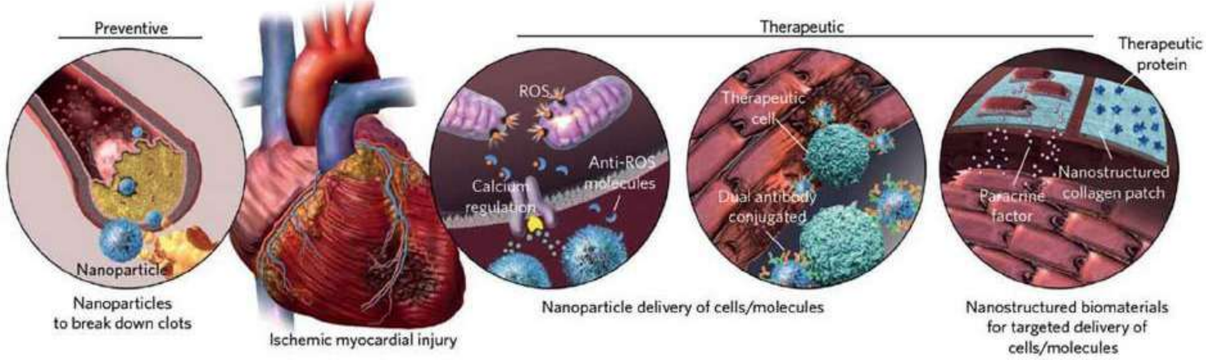

Figure 7: Applications of various nano platforms in the prevention and treatment of cardiovascular disease. *Nano platforms can target and break down coronary artery plaques and prevent injuries caused by stenosis or occlusion of arteries. Nanoparticulate systems can also reduce the adverse effects of reperfusion injuries and regenerate/salvage myocardium after MI, through sustained and targeted delivery of cells, biomolecules and paracrine factors. (© Nature Publishing Group)*

It can also be regarded as another implementation of nanotechnology in the field of medical sciences and diagnostics. One of the most important issues is the proper distribution of drugs and other therapeutic agents within the patient's body (Labhasetwar, 2005).

In the past two decades, however, researchers involved in the development of pharmaceuticals have understood that drug delivery is a fundamental part of drug development, and a wide range of drug delivery systems have thus been designed. Ideally, all these systems would improve the stability, absorption, and therapeutic concentration of the drug within the target tissue, as well as permit reproducible and long-term release of the drug at the target site (Kayser *et al.,* 2005). In addition to reducing the frequency of drug administration and thus improving patient comfort, novel drug delivery systems would offer protection and improve the pharmacokinetics of easily degradable peptides and proteins, which often have short half-lives in vivo (Orive *et al.,* 2003). For the pharmaceutical industry the field of drug delivery represents a strategic tool for expanding drug markets, because new delivery technologies could repackage classical drugs, offering a competitive edge after the expiry of patents and avoiding competition from generics. Demonstrating this advantage clearly, 13% of the current global pharmaceutical market is related to the sale of products that include a drug delivery system (Mazzola, 2003).

The final aim of pharmaceutical research is the delivery of any drug at the right time in a safe and reproducible manner to a specific target at the required level (Vasir and Labhasetwar, 2005; Parveen *et al.,* 2012).

Applications of nanotechnologies in medicine are especially promising, and areas such as disease diagnosis, drug delivery targeted at specific sites in the body, and molecular imaging are being intensively investigated and some products undergoing clinical trials (Shaffer, 2005). Nanotechnology is relatively new, and although the full scope of contributions of these technological advances in the field of human health care remains unexplored, recent advances suggest that nanotechnology will have a profound impact on disease prevention, diagnosis, and treatment (Li *et al.,* 2005).

In the near term, the most important clinical applications of nanotechnology are likely to be in pharmaceutical development. There are already an astonishing numbers of emerging applications (Jain, 2005). These applications either take advantage of the unique properties of nanoparticles as drugs or components of drugs per se or are designed for new approaches to controlled release, drug targeting, and salvage of drugs with low bioavailability. For example, nanoscale polymer capsules can be designed to break down and release drugs at controlled rates and to allow differential release in certain environments, such as an acid milieu, to promote uptake in tumors versus normal tissues. Substantial research is now designed for creating novel polymers and exploring specific drug-polymer combinations (Mayer, 2005).

Another broad application of nanotechnology is the delivery of antigens for vaccination (Koping-Hoggard *et al.,* 2005). Mucosal immunity is extremely important in disease prevention but continues to be limited by both degradation of the vaccine and limited uptake. Recent advances in encapsulation and development of suitable animal models have demonstrated that microparticles and nanoparticles are capable of enhancing immunization.

7. Gene delivery

Gene therapy is a recently introduced method for treatment or prevention of genetic disorders by correcting defective genes responsible for disease development based on the delivery of repaired genes or the replacement of incorrect ones (Ariga, 2006). The most common approach for correction of faulty genes is the insertion of a normal gene into a nonspecific location within the genome to replace a nonfunctional gene. An abnormal gene could also be swapped for a normal gene through homologous recombination or repaired through selective reverse mutation, which returns the gene to its normal function (Hanakawa *et al.,* 2005).

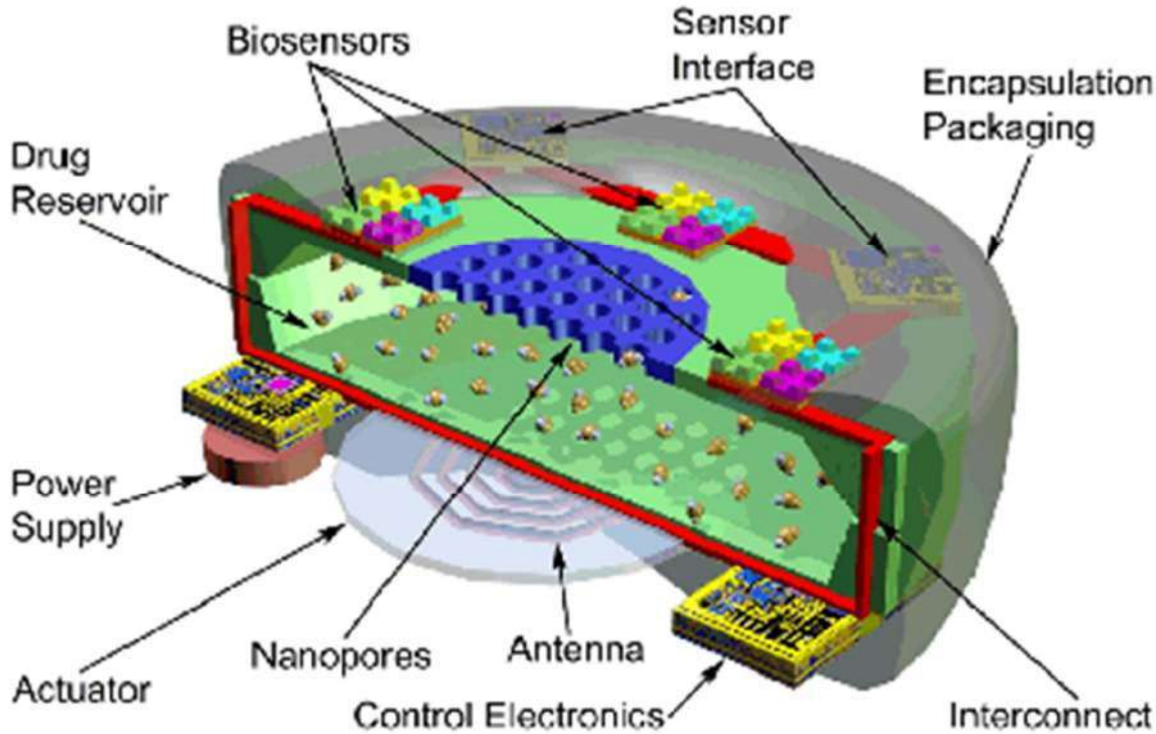

Figure 8: This figure shows an example an implantable drug delivery system for nanotechnology.

Three main types of gene delivery systems have been described: viral vectors, nonviral vectors (in the form of particles such as nanoparticles, liposomes, or dendrimers), and the direct injection of genetic materials into tissues using so-called gene guns (Verma and Weitzman, 2005).

AREAS OF CONCERNS IN NANOMEDICINE

There are valid arguments against the use of nanomedicine, particularly around the issue of toxicity. As explained in the *Scientific American* article "Nano-risks: A Big Need for a Little Testing". Elements at these microscopic levels can exhibit varying properties than they do normally. Furthermore, every nanoparticle is unique, and sometimes the combined effect of two of the same nanoparticles are not consistent. Thus, some nanoparticles may become dangerous for humans. It has been shown (Young and Martel, 2009) that even nanoparticles that naturally occur in our bodies can have deleterious effects on both our short and long term health. If these naturally created nanoparticles have the potential to cause harm, then before using artificially engineered ones, its possible effects and consequences should be considered. If nanomedicine is expanded to nanorobotics, then we would need to consider the possible effects of a glitch in the programming, and how severe the effects could be. This sounds a cautionary note that before nanomedicine can be used extensively, it will need to undergo series of testing processes to make sure it does not cause more harm than good.

Another disadvantage of nanotechnology is the enormous financial costs associated with it. As stated in a report by the Action Group on Erosion, Technology and Concentration (ETC) group, Nanotech Rx, *"the global health crisis doesn't stem from lack of scientific innovations or medical technologies; the root problem is poverty and inequality. New medical technologies are irrelevant for poor people if they are not accessible or affordable."* It is obvious that nanomedicine will definitely be too expensive for the average citizen, at least at first. It raises a question on whether we should focus instead on improving key aspects of the health system and providing better access to medicine and infrastructure to less developed countries than focusing on Nanomedicine. As the ETC says, *"access to clean water could make a greater contribution to global health than any single medical intervention in nanomedicine"* If we cannot maintain a working system using the current possibilities of medicine, should we not start by fixing what is wrong before looking at something new, and wasting billions of dollars in the process?

Finally, nanomedicine, like all technologies, can also be used for malicious purposes. Much of the proposed technology and treatment that nanomedicine will bring can be used for purposes other than that originally intended. This leads to problems of ethics and confidentiality. Nanorobots that could monitor the level of insulin in diabetics could also be misused by government and corporations monitor and increase surveillance of citizens. Such technology can also be used for military purposes. And where should we draw the line in the practical use of nanomedicine? To illustrate, if this technology allows us to heal people who have lost their vision or damaged their brains, either by an accident or through natural causes, should this technology be made available to the general public, allowing people to have biotech implants that give them superior vision or mental abilities? Should this be extended for military purposes? If so, then to what extent? There are many moral and ethical dilemmas regarding nanomedicine that must be answered before this technology is put to use.

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