

## Nanotechnology in Medicine: The Medicine of Tomorrow and Nanomedicine

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### Abstract

Nanotechnology is an emerging technology with enormous potential in information and communication technology, biology and biotechnology, medicine and medical technology. Novel nano- and bio-materials, and nanodevices are fabricated and controlled by nanotechnology tools and techniques, which investigate and tune the properties, responses and functions of living and non-living matter, at sizes below 100 nm. The current advances of nanotechnology in modern medicine are presented and discussed. The potential medical applications are predominantly in detection, diagnostics (disease diagnosis and imaging), monitoring, and therapeutics. The availability of more durable and better prosthetics, and new drug-delivery systems are of great scientific interest and give hope for cancer treatment and minimum invasive treatments for heart disease, diabetes and other diseases. Many novel nanoparticles and nanodevices are expected to be used, with an enormous positive impact on human health. The vision is to improve health by enhancing the efficacy and safety of nanosystems and nanodevices. Products based on nanotechnology in medicine and medical technology are reaching the market, with an anticipated enormous positive impact on human health, in the coming years. The development of specific guidance documents at a European level for the safety evaluation of nanotechnology products in medicine is strongly recommended and the need for further research in nanotoxicology, is identified. Ethical and moral concerns also need to be addressed in parallel with the new developments. *Hippokratia 2006; 10 (10):7-21*

**Key words:** *Nanotechnology, nanomedicine, nanobiotechnology, nanoparticles*

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### 1. Introduction

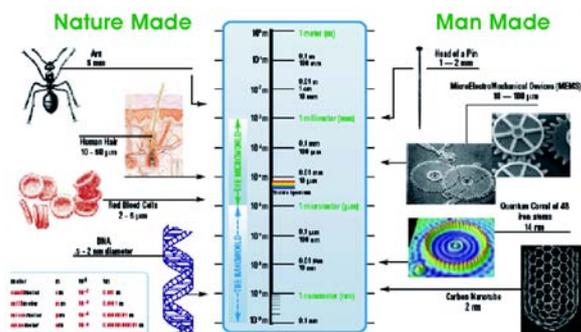
Nanoscale is generally considered to be at a size below 0.1  $\mu\text{m}$  or 100 nm (a nanometer is one billionth of a metre,  $10^{-9}$  m) (Figure 1). Nanoscale science (or nanoscience) studies the phenomena, properties and responses of materials at atomic, molecular and macromolecular scales, and in general at sizes between 1-100 nm. In this scale, and especially below 5 nm, the properties of matter differ significantly (i.e. quantum scale effects play an important role) from that at a larger particulate scale. Nanotechnology is then the design, the manipulation, the building, the production and application, by controlling the shape and size, the properties-responses and functionality of structures, devices and systems of the order or less than 100 nm.

Figure 1 shows objects and living units whose size is or occur basically in the nanoscale, are also shown higher order structures of biological units or organisms at micro- meso- and macroscale, made by nature the last 4 billion years due to the ability to self- assemble and self-organize. In the same figure (on the right) are shown those objects man made at nano- and microscale during the last few years. Nowadays, scientists and technologists are learning from nature, and by applying the laws

of physics, the properties of chemistry and the principles of biology, they create the era of nanotechnology.

Nanotechnology is considered an emerging technology due to the possibility to advance well established products and to create new products with totally new characteristics and functions with enormous potential in a wide range of applications. In addition to various industrial uses, great innovations are foreseen in information and communication technology, biology and biotechnology, medicine and medical technology, in metrology, etc. It is anticipated that nanotechnology can have an enormous positive impact on human health. Relevant processes of living organisms occur basically at nanometer scale, elementary biological units like DNA, proteins or cell membranes are of this dimension (Figure 1). By the means of nanotechnology, these biological units are going to be better comprehended so that they can be specifically guided or directed. Miniaturisation down to nanometer scale provides to become an essential feature of biomedical products and procedures in postgenomic era. Nanoscale devices could be 100 to 10,000 times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale

devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body.



**Figure 1.** Objects and living organisms whose size is or occur in the nanoscale, higher order structures of biological units at micro- meso- and macroscale, made by nature the last 4 billion years due to the ability to self-organize (on the left) and those man made at nano- and microscale the last few years (on the right).

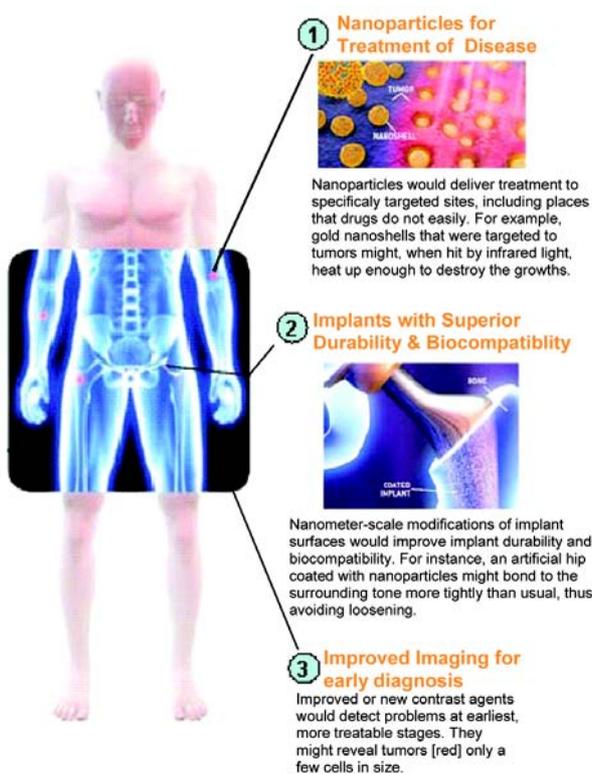
Huge aspirations are coupled to nanotechnological developments in modern medicine (Nanotechnology, Biotechnology, Information Technology & Cognitive Science - NBIC developments). The potential medical applications are predominantly in diagnostics (disease diagnosis and imaging), monitoring, the availability of more durable and better prosthetics, and new drug-delivery systems for potentially harmful drugs<sup>1</sup>, as shown in Figure 2. For example, nanoscaled diagnostics are expected to identify in the becoming, giving the opportunity to intervene specifically prior to a symptomatically detected onset disease.

Biomedical nanotechnology presents revolutionary opportunities in the fight against many diseases. An area with near-term potential is detecting molecules associated with diseases such as cancer, diabetes mellitus, neurodegenerative diseases, as well as detecting microorganisms and viruses associated with infections, such as pathogenic bacteria, fungi, and HIV viruses. For example, in the field of cancer therapy, promising novel nanoparticles will respond to externally applied physical stimuli in ways that make them suitable therapeutics or therapeutic delivery systems. Another important field of application for nanotechnology are biomaterials used for example in orthopedic implants or as scaffolds for tissue engineered products. Nanotechnology might yield nano-structured surfaces preventing non-specific protein adsorption. Control of surface properties at nanolevel was shown to increase the biocompatibility of the materials<sup>2</sup>.

While products based on nanotechnology are actually reaching the market, sufficient knowledge on the associated toxicological risks is still lacking. Reducing the size of structures to nanolevel results in distinctly different properties. As well as the chemical composition, which largely dictates the intrinsic toxic properties,

very small size appears to be a dominant indicator for drastic or toxic effects of particles. From a regulatory point of view, a risk management strategy is already a requirement for all medical technology applications<sup>1</sup>.

In order to discuss the advances of nanotechnology in modern medicine, we present in Section 1 the terms and concepts of nanoscale and nanotechnology, and the relevant process and relation to living units. The impact of nanomaterials and nanoparticles in medicine is presented in Section 2, following by a description of nanotechnology tools in medicine in Section 3. The impact of nanotechnology in medicine and medical technology is presented in Section 4, first with the introduction of nanomedicine and the “nanorobots”, and then through some of myriad applications in diagnosis and treatment (such as biocompatibility and implants, cardiology, cancer, theranostics, etc). In Section 5, a reference to the possible risks for human health and a consideration of ethical questions is given.



**Figure 2.** Great developments are expected in medicine with the use of nanotechnology, such as: 1) use of nanoparticles for the treatment of diseases, 2) implants with superior durability and biocompatibility, 3) improved imaging for early diagnosis.

## 2. Nanomaterials and nanoparticles in medicine: A new concept

Novel nanomaterials and nanoparticles are envisaged to have a major impact on a number of different relevant areas. Materials with high performance and unique properties can be produced, that traditional synthesis and manufacturing methods could not create.

Future nanoparticles should act as drug-delivery and drug-targeting systems. Due to their smallness they are not recognized by the human body, migrate through cell membranes beneath a critical size and are able to pass the blood-brain barrier. These characteristics are used to develop nanoscaled ferries, which transport high potential pharmaceuticals precisely to their destination. There are different kinds of nanoparticles which are suitable to be applicable in drug- and gene-delivery, probing DNA structures, etc, and are categorized as: liposomes, polymer nanoparticles (nanospheres and nanocapsules), solid lipid nanoparticles, nanocrystals, polymer therapeutics such as dendrimers, fullerenes (most common as C60 or buckyball, similar in size of hormones and peptide  $\alpha$ -helices), inorganic nanoparticles (e.g. gold and magnetic nanoparticles).

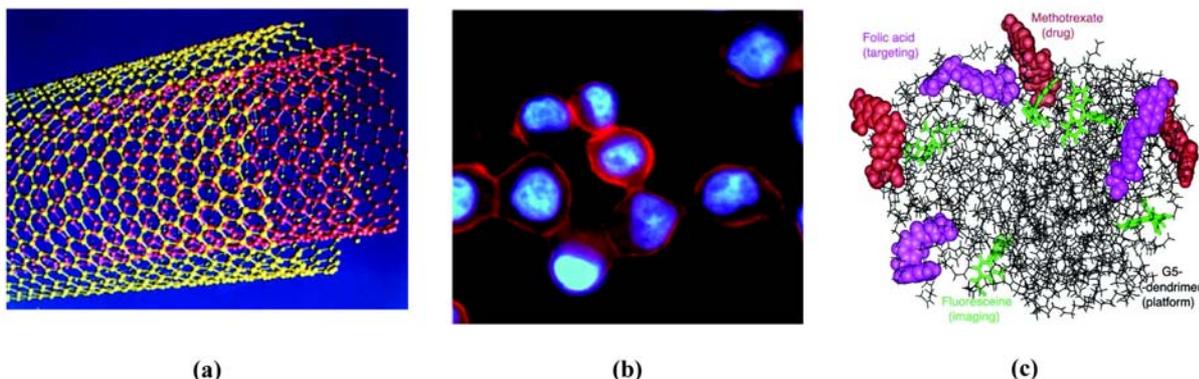
*Carbon nanotubes* (diameter of 1-20 nm, as shown in Figure 3a) and *inorganic nanowires* exhibit extraordinary mechanical, electric, electronic, thermal, and optical properties offering the electronic industry properties that few materials platforms could ever hope to match. Carbon nanotubes, and magnetic iron oxide nanoparticles, gold-coated silica nanoshells, can transform electro-magnetic energy into heat, causing a temperature increase lethal to cancer cells merely by increasing the magnetic field or by irradiation with an external laser source of near infra red light at the very location where these nanoparticles are bound to or internalised within tumour cells<sup>2</sup>.

*Quantum dots* (nanometer sized semiconductor nanocrystals with superior fluorescent properties, as shown in Figure 3b) possess remarkable optical and electronic properties that can be precisely tuned by changing their size and composition, due to their very small size (2-10 nm). Due to their relatively inexpensive and simple synthesis, quantum dots have already entered the market for experimental biomedical imaging applications. Quantum dots can be made to emit light at any wavelength in the visible and infrared ranges, and can be inserted almost anywhere, including liquid solution, dyes etc. Quantum dots can be attached to a variety of surface ligands, and inserted into a variety of organisms for in-vivo research<sup>2,3</sup>.

*Dendrimers* (complex almost spherical macromolecules with diameter 1-10 nm, shown in Fig.3c) have improved physical, chemical, and biological properties compared to traditional polymers. Some unique properties are related to their globular shape and the presence of internal cavities offering the possibility as medical nanovehicles. Dendrimers have a tree-like structure with many branches where a variety of molecules, including drugs can be attached. Less than 5 nm in diameter, dendrimers are small enough to slip through tiny openings in cell membranes and to pass vascular pores and tissues in a more efficient way than bigger polymer particles. In experiments reported in Cancer Research, University of Michigan scientists attached methotrexate, a powerful anticancer drug, to branches of the dendrimer (Figure 3c). On other branches, they attached fluorescent imaging agents and a vitamin called folic acid<sup>2,3</sup>.

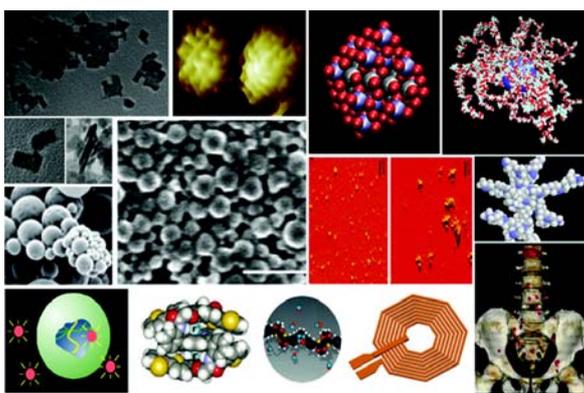
In addition to these examples of individual nanoparticles, novel biomaterials can be constructed using structural surface modifications of macro-, micro- as well as nanomaterials. Control of surface properties at nanolevel was shown to increase the biocompatibility of the materials<sup>2</sup>.

Nanoparticles, as shown in Figure 4, being the fundamental elements of nanotechnology, can be applied in various ways such as fluorescent biological markers, as markers for detection of proteins, probing of DNA structures and for separation and purification of biological molecules and cells, and they can also be used for magnetic resonance imaging enhancement, tumour destruction via heating, tissue engineering and drug, gene delivery. As an example, two kinds of nanoparticles that are suitable to be applicable at least in drug-delivery will be described: First, gold nanoparticles (3-20 nm), that are gold composites with dielectrical cores and golden shells. By choosing the right ratio of core to shell diameters the particle can be tuned to absorb highly in the near infrared, and by irradiation with such wavelength can be heated, even in deeper skin areas. If the particles are embedded in a temperature sensible hydrogenmatrix, the matrix will collapse and the included agents will be released at a critical temperature.



**Figure 3.** Representative types of nanomaterials and nanoparticles: a) Carbon nanotube, b) Human breast cancer cells tagged with quantum dots, and c) Dendrimer [3].

Second, magnetic nanoparticles, with controllable sizes between 2-30 nm that can be coated with biological molecules to make them interact with or bind to a biological entity. Due to their magnetism they can be manipulated by an external magnetic field gradient, thereby providing a controllable means of “tagging” or addressing the biological entity. They can be made to deliver a package (an anticancer drug, or a cohort of radionuclide atoms) to a targeted region of the body. The magnetic particles can be provided with energy from the exciting external field, and can be heated up making them good hyperthermia agents, delivering toxic amounts of thermal energy to targeted bodies, such as tumours.



**Figure 4.** Various nanoparticles and dendrites and their medical applications.

For applications to medicine and physiology, these nanomaterials, nanoparticles and devices can be designed to interact with cells and tissues at a molecular (i.e., sub-cellular) level with a high degree of functional specificity, thus allowing a degree of integration between technology and biological systems not previously attainable. It should be appreciated that nanotechnology is not in itself a single emerging scientific discipline but rather a meeting of traditional sciences such as chemistry, physics, materials science, and biology to bring together the required collective expertise needed to develop these novel technologies<sup>4</sup>. On the other hand, due to advances in biochemical research and molecular biology diseases can be put down to molecular abnormalities. Molecular imaging should detect the corresponding molecular signatures of diseases and use it for medical diagnosis. This should ideally lead to a diagnosis and therapy before occurrence of symptoms. In molecular imaging, an imaging molecule is coupled to a transport molecule or particle, which possesses a targeting unit (e.g. special receptors, ligands or peptides). The target finding system should be a specific molecular marker of a certain disease thus the contrast medium accumulates within the sick tissue. Molecular imaging is developed for several diagnostic procedures such as magnetic resonance, ultrasonic imaging, as well as nuclear and optical imaging technologies.

### 3. Nanotechnology Tools in Medicine

Different methods for the synthesis of nanoengineered materials and devices can accommodate precursors from solid, liquid or gas phases and encompass a tremendously varied set of experimental techniques. A detailed presentation of these are beyond the scope of this review. In general, however, most synthetic methods can be classified into two main approaches: “top-down” and “bottom-up” approaches and combinations of them. “Top-down” (photolithography, microcontact printing) techniques begin with a macroscopic material or group of materials and incorporate smaller-scale details into them, whereas “bottom-up” (organic-synthesis, self-assembly) approaches, begin by designing and synthesizing custom-made molecules that have the ability to self-assemble or self-organize into higher order mesoscale and macroscale structures<sup>4</sup>.

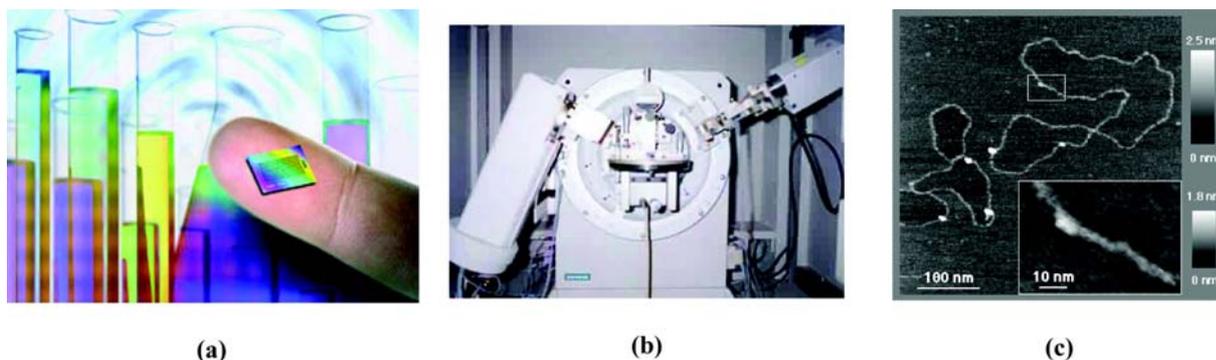
There are several nanotechnology-based synthesis techniques of these materials. For example, carbon nanotubes, are developed by electric arc discharge, laser ablation, and chemical vapour deposition techniques. Various inorganic nanotubes are developed by arc discharge, and laser ablation, as well as through appropriate chemical reactions. Nanowire properties can differ distinctly from those of their corresponding crystalline bulk materials, though, some properties are similar. Nanowires can be synthesized using a large variety of materials such as metals, e.g. Ag, semimetals, e.g. Bi, semiconductors, e.g. CdS, and superconductors. The most common synthesis methods are template-assisted synthesis, including vapour and electrochemical deposition, and vapour-liquid-solid growth, especially successful for semiconductor nanowires. Dendrimers were first synthesized by an iterative synthetic methodology. The iterative sequence of reaction steps leads to a higher generation dendrimer after each iteration. The creation of dendrimers, using specifically-designed chemical reactions, is one of the best examples of controlled hierarchical synthesis, an approach that allows the “bottom-up” creation of complex systems. The functional end groups can be modified for various purposes, including sensing, catalysis or biochemical activity.

Other advanced applications of micro- and nanotechnology in medicine are the microchip-based drug delivery systems, which are devices incorporating micrometer-scale pumps, valves and flow channels. They allow controlled release of single or multiple drugs on demand. Micro- and nanotechnology-based methods (e.g., UV-photolithography, reactive ion etching, chemical vapour deposition, electron beam evaporation) can be used for the fabrication of these silicon-based chips.

A myriad of studies is available for applications of micro- and nanotechnologies in chips for medical molecular diagnostics. Key words are for example DNA microarrays (gene chips), protein microarrays (protein chips), lab-on-a-chip devices (Figure 5a), and cell chips. Basically, these devices or systems are constructed using techniques inspired from micro/nanoscale fabrication

methods, that are used for processing, manipulation, delivery, analysis or construction of biological and chemical entities. Inkjet printing methods are used in DNA microarrays for human genomics and in protein microarrays (or protein chips), which are useful for molecular diagnostics. For the subsequent readout detection either fluorescence- or radionuclide-based markers, or surface plasmon resonance spectroscopy can be applied<sup>2</sup>.

the diagnosis of human diseases. Imaging at cellular, and even sub-cellular and molecular level, is still largely a domain of basic research. However, it is anticipated that these techniques will find their way into routine clinical use. Atomic force microscopy (AFM) and AFM-related techniques (e.g. Scanning Near-Field Optical Microscopy-SNOM) have become sophisticated tools, not only to image surfaces of molecules or sub-cellular compartments, but also to measure molecular forces

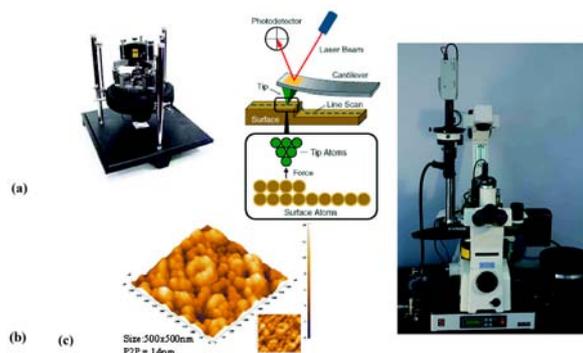


**Figure 5.** a) Lab-on-a-chip, for quick test results using very small samples. A lab-on-a-chip miniaturises all the steps needed to process a medical sample and detect disease, b) X-Ray Diffractometer of the Laboratory for Thin Films – Nanosystems & Nanometrology of AUTH, c) Plasmid DNA, prepared on mica (an insulator) imaged with STM in humid air<sup>5</sup>.

In order to study and explore these rich and complex systems, highly sophisticated experimental, theoretical and modelling tools are required. Especially, the visualization, characterization, and manipulation of materials and devices require sophisticated imaging and quantitative techniques with spatial and temporal resolutions on the order of  $10^{-6}$  (a micron – a red cell is 7 microns) and below to the molecular level. In addition, these techniques are critical for understanding the relationship and interface between nanoscopic and mesoscopic/macrosopic scales, a particularly important objective for biological and medical applications. As such, further nanotechnological advances will necessitate parallel progress of these physical characterization techniques. Examples of important tools available at the moment include: highly focused (i.e., 1–2  $\mu\text{m}$ ) synchrotron X-ray sources and related techniques that provide detailed molecular structural information by directly probing the atomic arrangement of atoms (Figure 5b); scanning probe microscopy (STM, AFM) that allow three dimensional-type topographical atomic and molecular views or optical responses (SNOM) of nanoscale structures (Figure 5c); in situ monitoring techniques that allow the monitoring and evaluation of building block assembly and growth<sup>13</sup>; ellipsometry, an optical method, with the capability of measuring in liquid environment (e.g. protein solution) to study protein and cells adsorption on solid surfaces<sup>6</sup>, it has been employed to discriminate and identify bacteria at the species level, and is very promising for analytical purposes in biochemistry and in medicine<sup>6,7</sup>.

Imaging is becoming an ever more important tool in

between molecules. This is substantially increasing our knowledge of molecular interactions<sup>8</sup>. Figures 6a and 6b, show the SNOM and AFM microscopes, respectively. Figure 6c is an AFM topography image of a cluster of fibrinogen molecules adsorbed on amorphous carbon thin film, after incubation of 5min. The adsorbed cluster has preserved the morphological characteristics of the protein molecule<sup>9</sup>. Through these techniques, protein adsorption is studied, in order to shed some light and to understand its mechanism, and improve the properties of the potential materials and coatings that are going to be used for biomedical applications.



**Figure 6.** a) Atomic Force Microscope and how AFM works<sup>5</sup>, b) AFM topography image of fibrinogen on amorphous carbon thin film after 5min incubation time, with a 500x500nm size focus on one of the fibrinogen molecular cluster – shape features (Inset: the 2D equivalent image) and c) Scanning Near-Field Optical Microscope for reflection and fluorescence from scales below 50nm<sup>5,9,10</sup>.

Scientists have developed analytical tools to examine the biological cells in great details. We now understand better how biological structures function in general intracellular level. However, we still do not know how to build nanostructures or “nano” biomachines that are compatible (i.e. biocompatible) with living organ, tissues, cells and biochemical systems, so that they safely operate inside the body. Once these questions are answered, we will be able to design better diagnostic tools and engineer structures for better treatments of diseases.

#### 4. Medical Applications of Nanotechnology and Nanomedicine

Nanotechnology offers important new tools with a great impact on many areas in medical technology.

It provides extraordinary opportunities not only to improve materials and medical devices but also to create new “smart” devices and technologies where existing and more conventional technologies may be reaching their limits. In the following these definitions related with new research areas and terms (i.e. nanobiotechnology, nanomedicine, nanodevices, “nanorobots”) will be given and then some of myriad applications of nanotechnology in modern medicine will be discussed in more detail.

**Nanomedicine:** The convergence of recent advances in nanotechnology with modern biology and medicine has created the new research domain of nanobiotechnology. The use of nanobiotechnology in medicine is termed nanomedicine. Thus, nanomedicine

is an offshoot of Nanotechnology, referring to highly specific medical intervention at the molecular scale for *therapeutic purposes* (involving curing diseases or repairing damaged tissues), and for the development of *diagnostics* for rapid monitoring, targeted cancer therapies, localized drug delivery, improved cell material interactions, scaffolds for tissue engineering, and gene delivery systems. Successful research and development in nanomedicine where ultimately patients can benefit from these new technologies require the interaction of a multitude of disciplines including material science and engineering, cellular biology and clinical translational research.

Many scientific as well as economic activities are expected to accelerate medical research and development. Several medical devices<sup>2</sup> have already benefited from recent developments in micro- nanotechnology (see Table 1) and are in use or are currently being commercialized (Figures 5 and 7).

Nanomaterials and biological structures are approximately of the same size, which allows for unique interactions between biological systems and synthetic materials for analytical, diagnostic and therapeutic applications.

Nanomedicine can focus on several topics, such as: *Engineering Topics* including, for example, Peptide nanoparticles for medical applications, the Transition from semiconductors to biochemistry in the lithography industry; *Clinical Applications* (like nanomedicine and protein misfolding diseases); *Topics in genetics* (e.g. Nanostructured probes for gene detection in living cells, Detecting UV damage to individual DNA molecules with

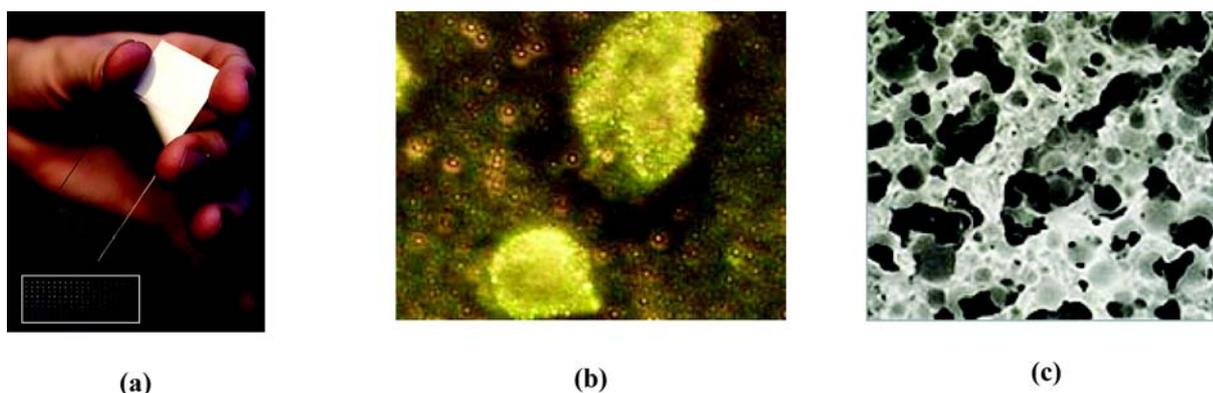
**Table 1.** Medical devices and applications currently evaluated in clinical investigations or expected to enter clinical research in the near future.

Micro- & Nanotechnology in Medicine	Year
<ul style="list-style-type: none"> <li>• Surgical tools</li> <li>• Microcantilevers for label-free assays used in molecular in vitro diagnostics</li> <li>• Novel nano-sized contrast agents for molecular imaging</li> <li>• Bone replacement materials, pacemakers and hearing aids</li> <li>• DNA/protein microarrays and lab-on-a-chip devices for molecular in vitro diagnostics</li> <li>• Wound dressings and textiles with antibacterial and fungicidal activity</li> <li>• Microneedle-based systems</li> <li>• Superparamagnetic iron oxide nanoparticles administered by stereotactic navigation based injection (hyperthermia treatment of brain/prostate tumours)</li> <li>• Si-based nanocarrier system incorporating a radionuclide (treatment of tumours via brachytherapy)</li> <li>• Retinal prostheses (restoration of vision in blind patients)</li> </ul>	now
<ul style="list-style-type: none"> <li>• Stents coated with nanoporous hydroxyapatite</li> </ul>	2006
<ul style="list-style-type: none"> <li>• Superparamagnetic iron oxide nanoparticles conjugated with monoclonal antibodies</li> <li>• Injected intravenously for selective, targeted radiotherapy to treat tumours</li> </ul>	2007
<ul style="list-style-type: none"> <li>• Dendrimer-based nanoplatfoms capable of delivering drugs and genes to specific targeted cells with imaging/monitoring modality</li> </ul>	2008
<ul style="list-style-type: none"> <li>• Targeted sensitizer nanoparticles physically triggered using heat, magnetic field, light, or radiation for tumour treatment</li> </ul>	

Atomic Force Microscopy, etc); *Topics in Diagnostics*, with its main focus on early diagnosis in vitro and in vivo; *Policy and Commercialization Topics*, including initiative in nanomedicine to focus efforts in research, development and applied nanotechnology for improving the diagnostics, therapeutics and treatment of cancer; *Experimental Research Topics*, which are an important basis for preclinical study, like Nanodiagnostic imaging; *Topics on Basic Nanomedicine*, *Pharmacology Topics*; *Topics on Oncology and on Toxicology*<sup>11</sup>.

found in the human bloodstream using a digest and discharge protocol. Microbivores are expected to be up to 1000 times faster acting than either unaided natural or antibiotic assisted biologic phagocytic defenses and able to extend the therapeutic competence of the physician to the entire range of potential bacterial threats, including locally dense infections. The “microbivores” would be removed from the body once their mission was completed.

Medical “nanorobots” may also be able to intervene



**Figure 7.** a) DNA-chip: glass plate containing thousands of genes to be studied. Comparison of its size with a human hand. Inset: glass plate detail, b) Image of gold nanoparticles sticking to cancer cells and c) Electron microscope image of highly porous OSferion, an artificial bone replacement material with excellent biocompatibility<sup>13</sup>.

The long-term goal of nanomedicine research is to characterize quantitative molecular-scale components known as nanomachinery, as well as to precisely control and manipulate nanomachinery in cells to improve human health, understand the cellular mechanisms in living cells, and develop advanced technologies for early diagnosis and treatment of various diseases. This far the assessment of single –molecule properties in living cells has been restricted by either the size of the probe or the photobleaching of the small fluorescent labels. The significance of this research lies in the development of a platform technology that will influence nanoscale imaging approaches designed to probe molecular mechanisms in living cells.

**“Nanorobots” and nanodevices:** Such future devices are, for example, the artificial mechanical red blood cell or “respirocyte” (spherical shape of 1 $\mu$ m diameter) and an artificial mechanical white blood cell of microscopic size, called a “microbivore” (3.4  $\mu$ m major axis diameter and 2.0 $\mu$ m minor axis diameter). The “respirocyte” is expected to be able to deliver more oxygen to the tissues than natural red blood cells and to manage carbonic acidity. Primary medical applications of respirocytes would include transfusable blood substitution; partial treatment for anemia, lung disorders, enhancement of cardiovascular/neurovascular procedures, tumour therapies and diagnostics, prevention of asphyxia, artificial breathing, and a variety of sports, veterinary and battlefield. The primary function of “microbivore” is to destroy microbiologic pathogens

at the cellular level, performing in-vivo cytosurgery. The most likely site of pathologic function in the cell is the nucleus – more specifically, the chromosomes. In one simple cytosurgical procedure called “chromosome replacement therapy”, a “nanorobot” controlled by a physician would extract existing chromosomes from a particular diseased cell and insert new ones in their place, in that same cell. If the patient chooses, inherited defective genes could be replaced with non defective base-pair sequences, permanently curing a genetic disease. Engineered bacterial “biobots” (synthetic microbes) may be designed to produce useful vitamins, hormones, enzymes or cytokines in which a patient’s body was deficient or to selectively absorb and metabolize harmful substances such as poisons, toxins etc into harmless end products<sup>12</sup>.

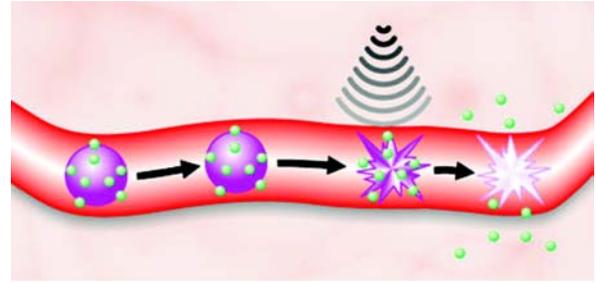
**Biocompatibility and Orthopedic implants:** An important field of application for nanotechnology in medicine is the biomaterials, used for example in orthopedic implants or as scaffolds for tissue engineered products. If the design of a hip implant, for instance (Figure 2), is carried out at nanolevel, it might become possible to construct an implant which closely mimics the mechanical properties of human bone, preventing stress-shielding and the subsequent loss of surrounding bone tissue<sup>2</sup>. Extra-cellular matrix (ECM) provides an excellent three-dimensional web of intricate nanofibers to support cells and present an instructive background to guide their behaviour. It takes a variety of forms in different tissues and at

different stages of development in the same tissue. This diversity arises through combinations of specific molecular interactions and geometrical arrangements of collagens, elastins, proteoglycans, and adhesion proteins, such as fibronectins and laminins. Unwinding the fibers of ECM, reveals a level of detail unmatched outside the biological world. Each fiber hides clues that pave the way for cells to form tissues, as complex as bone, liver, heart and kidney. A key challenge is to capture the degree of complexity that is needed to functionally replicate the ECM of natural tissue. Nevertheless, we are still a long way from recreating the molecular architecture of the ECM and the dynamic mechanisms by which information is revealed in response to challenges within the local environment. Nanostructuring of materials provides a powerful mechanism to encourage and direct cell behaviour, ranging from cell adhesion to gene expression, thus enhancing their biocompatibility, by dictating the desirable interactions between cells and materials.

The question of how cells detect and respond to nanofeatures is unresolved yet. However, there are early findings, where the promotion of one cell type over another, such as osteoblasts (bone-forming cells) over osteoclasts (bone-resorbing cells), to stimulate bone growth, will be important in reducing aseptic loosening and failure of implants. It has been found that not only the scale of topography (5 nm to micrometer scale) modulates cell behaviour, but also the type of ordered topography (e.g., ridges, steps, grooves, pillars, and pits) and even their symmetry (e.g., orthogonal or hexagonal packing of nanopits)<sup>32</sup>. Furthermore, surface modifications at nanolevel of biomaterials or their coatings might greatly enhance the biocompatibility by favouring the interaction of living cells with the biomaterial, especially by their beneficial effect on cell adhesion and proliferation. Together with the control of nanoporosity allowing vascularisation and the growth of cells inside the biomaterial, the nano-structured surfaces of biomaterials also allow the creation of novel types of scaffolds for tissue-engineered products<sup>2</sup>.

**Nanotechnology in Cardiology:** Nanotechnology has various applications in the field of cardiology research not only for diagnostic but also for therapeutical purposes<sup>14</sup>.

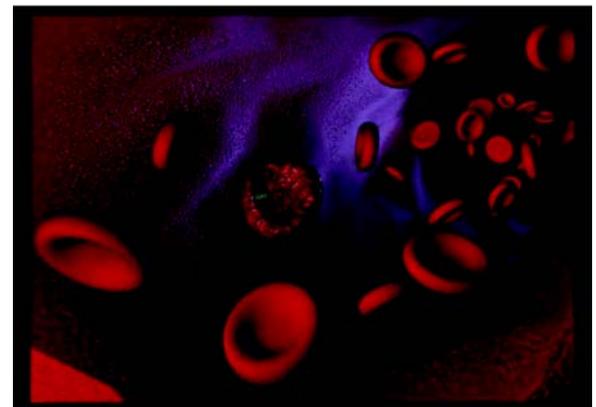
On the therapeutical scope, minimally invasive treatments for heart disease, diabetes and other diseases is a desirable goal for scientists, and there is hope for it, because of the use of nanotechnology. More precisely, a team led by Paul Grayburn of Baylor University Medical Center, and Ralph Shohet of the University of Texas Southwestern Medical School, in Dallas, Texas, has demonstrated that ultrasound-targeted microbubble destruction (Figure 8) can deliver genes that stimulate the growth of new blood vessels in rat heart<sup>15</sup>.



**Figure 8.** Gas-filled microbubbles (purple) covered with DNA (green) pass harmlessly and uneventfully through blood vessels until they are exposed to ultrasound. Then, the bubbles burst, causing not only the release of the DNA but also the opening of holes in the cells that line the vessel<sup>15</sup>.

**Cardiovascular gene therapy** could be realized roughly as follows: identification of a protein whose presence causes blood vessels to form, production and packaging of strands of DNA that contain the gene for making the protein and deliverance of the DNA to heart muscle. Of those steps, the last is the most challenging. In the late 1990s, physicians and physicists hit on the idea of using ultrasound contrast agents to deliver DNA, which can be seen in Figure 8. If the ultrasound is intense enough, the bubbles can burst with sufficient force to breach the membranes of nearby cells. And if the bubbles are coated with DNA, their destruction releases the DNA, enabling it to enter the cells through the holes forced open by the burst<sup>15</sup>.

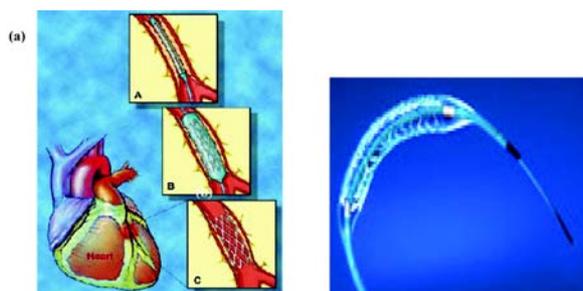
**“Bibots”** (a kind of nanorobots), another application of nanotechnology, is the creation of muscle-powered nanoparticles having the ability to transfer information into cells, gives the potential of replacing lost biological function of many tissues such as sinoatrial node. This effect can lead to treatment of diseases which otherwise would be fatal or difficult to cure for human beings (Figure 9).



**Figure 9.** A futuristic representation of a “Bibot” in the area of a red cell within a blood vessel.

Nanotechnology also plays a key role in the interventional therapeutic approach of *atherosclerosis*

and *Coronary Artery disease* (CAD), by improving the biocompatibility of intracoronary stents and by regulating the main limit factors for *Percutaneous Transluminal Coronary Angioplasty* (PTCA) at a molecular level via nanoparticles (Figure 10a). The PTCA introduced in the late 1970s and has been one of the most important treatment strategies for CAD and its landmarks were the implantation of a metallic stent introduced in the late 1980s and the production of drug - eluting stents (Figure 10b) in the early 2000s.



**Figure 10.** a) Percutaneous transluminal coronary angioplasty with stent implantation b) Drug - eluting stent.

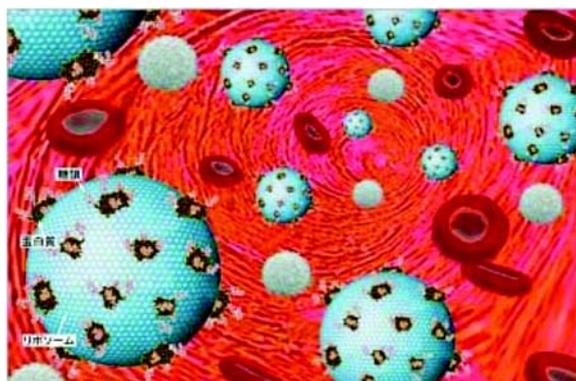
The major drawback of PTCA has been the occurrence of restenosis of the treated vessels, due to neointima proliferation and the negative remodelling of the artery, resulting in renewed symptoms and the need for repeated intervention in up to 50% of patients. The introduction of intracoronary bare metal stents reduced the restenosis rate within 6 months, however a smaller portion of the patients (20–30%) still suffered of so called “in-stent” restenosis. Recently, drug-eluting stents loaded with the anti-proliferative compounds paclitaxel and rapamycin have lead to the reduction of restenosis rate to 1–3% at 1 year.

However, “in-stent” restenosis remains the major limiting factor of percutaneous interventions for Coronary Artery Disease. That is the reason that makes nanotechnology necessary for improving biocompatibility of stents. Many nanocoatings have been evaluated in-vivo and in-vitro and have been proposed to improve the biocompatibility of metallic stents or to serve as matrix for drug delivery.

Recent research data involving surface modifications of these prostheses at nanoscale as well as the loading of an antiproliferative and anti-inflammatory drug onto a stent via nanoparticles such as liposomes may lead to the prevention of early thrombus formation and late neointima development, which are the major side effects of PTCA with stent implantation<sup>16</sup>.

Going beyond drug-eluting stents, many nanoparticle carrier systems may be developed in order to transfer molecules via blood stream that block both neointimal hyperplasia and negative remodeling. In Figure 11, we can see these molecules that can be used as stand-alone and without being necessary to be loaded onto stents and their potential molecular targets could be endothe-

lial cells, vascular smooth muscle cells, adventitial fibroblasts, leukocytes and platelets which are the main cells involving in acute thrombosis and neointimal hyperplasia after PTCA with stent implantation.



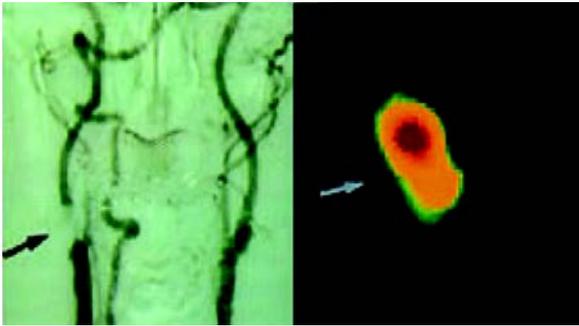
**Figure 11.** Molecules such as drugs targeting the area of arterial wall being undergone PTCA with stent implantation.

In particular, in a mouse model of vascular injury, the injection of endothelial progenitor cells was associated with endothelization of the injured segment of the artery and with reduced neointimal proliferation. Many antiapoptotic agents such as caspase inhibitor or an antiapoptotic gene targeting against the activation of vascular smooth muscle cells, transferring via nanoparticles to the arterial wall being injured by stent implantation, might reduce restenosis.

In general, various inhibitors of growth factors secreted by activated platelets such as PDGF, Il-1, TGF- $\beta$  and inhibitors of proinflammatory agents relased by leucocytes upon activation (e.g monocyte chemoattractant protein-1) could be used as antithrombotic and antirestenotic agents. It can be concluded that a highly effective molecular coronary intervention by means of nanotechnology may eliminate the need for stents themselves<sup>17</sup>.

*Diagnosis of cardiovascular diseases* is an application of recent advances in nanotechnology as well. Many monoclonal antibodies, peptides and carbohydrates for non-invasive targeting of atherosclerotic lesions, myocardial necrosis, brain infarction and various tumours can be used for their detection. As an example, an antibody specific for the proliferating smooth muscle cells of the human atherosclerotic plaque was standardized for imaging experimentally-induced atherosclerotic lesions in rabbits. The antibody after successful preclinical trials in Northeastern University is already being used for clinical studies in Italy and Spain<sup>18</sup>. Figure 12 illustrates very small atherosclerotic lesions in-vivo, using bispecific antibodies targeted with very high specific-radioactivity nano-polymers.

*The detection of the complementary DNA strand* is another application of nanotechnology in the field of cardiology, that is based on the discovery of complexes of single-walled Carbon nanotubes with single-stranded



**Figure 12.** Atherosclerotic lesions labelled by Bispecific antibodies targeted with very high specific-radioactivity nano-polymers<sup>14</sup>.

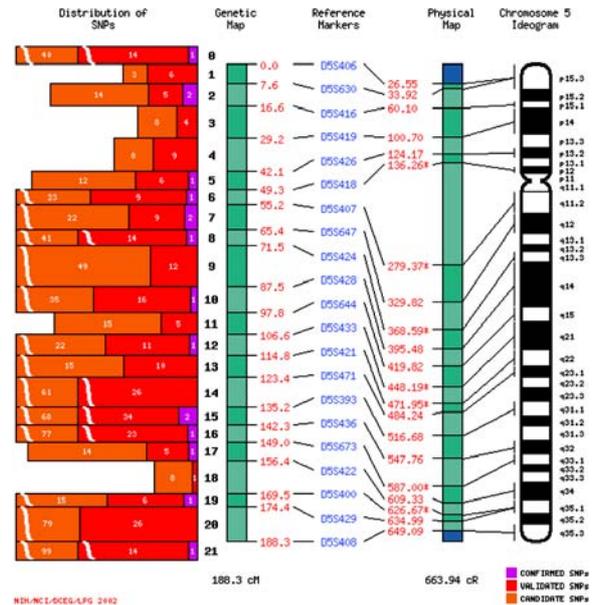
DNA<sup>19</sup>. If a single nucleotide alteration occurs, the association between the carbon nanotube and the complementary DNA strand will be changed, resulting in the detection of single-nucleotide polymorphisms (SNPs). SNPs are sites in the human genome where individuals differ in their DNA sequence, often by a single base. These slight variations in DNA sequences can have a major impact on whether or not a person may develop a disease and even influence the response to drug regimens. Researchers in public and private sectors are generating SNPs maps which can occur in genes as well as in noncoding regions. Figure 13, illustrates an example of a SNP map of human Chromosome 5<sup>20</sup>.

Scientists believe that these maps will be used for the identification of the multiple genes associated with complex diseases such as Coronary Artery Disease (for example, ABCA1 gene is susceptible for CAD), hyperlipideamia, cancer, diabetes melitus and to detect humans with genetic predisposition to these diseases<sup>21</sup>.

By screening tests which are based on the above application of Nanomedicine, individuals that are prone to develop atherosclerosis might be detected and by controlling the main risk factors for CAD (hypertension, diabetes mellitus, smoking, hyperlipideamia, obesity) a long-term acute coronary syndrome may be avoided<sup>22</sup>. This approach can also be used for a variety of other diseases, leading to the earlier diagnosis and prevention.

**Nanotechnology against Cancer:** Nanotechnology may have an impact on the key challenges in cancer diagnosis and therapy. Diagnosing, treating, and tracking the progress of therapy for each type of cancer has long been a dream among oncologists, and one that has grown closer thanks to parallel revolutions in genomics, proteomics and cell biology. Nanotechnology's greatest advantage over conventional therapies may be the ability to combine more than one function.

Recently, there is a lot of research going on to design novel *nanodevices* capable of detecting cancer at its earliest stages, pinpointing it's location within the hu-



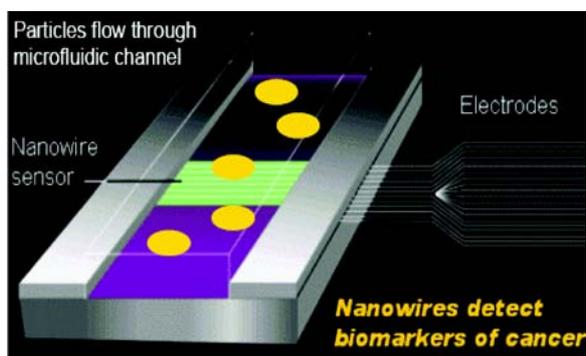
**Figure 13.** An example of a single-nucleotide polymorphisms - SNPs map of human Chromosome 5.

man body and delivering chemotherapeutic drugs against malignant cells. The major areas in which nanomedicine is being developed in cancer involve: a) **early detection of tumour** (developing "smart" collection platforms for simultaneous analysis of cancer-associated markers and designing contrast agents that improve the resolution of tumour area comparing with the nearby normal tissues), and b) **cancer treatment** (creating nanodevices that can release chemotherapeutic agents).

**Tumour diagnostics** and prevention is the best cure for cancer, but failing that, early detection will greatly increase survival rates with the reasonable assumption that an in situ tumour will be easier to eradicate than one that has metastasized. Nanodevices and especially nanowires can detect cancer-related molecules, contributing to the early diagnosis of tumour. Nanowires having the unique properties of selectivity and specificity, can be designed to sense molecular markers of malignant cells. They are laid down across a microfluidic channel and they allow cells or particles to flow through it. Nanowires can be coated with a probe such as an antibody or oligonucleotide, a short stretch of DNA that can be used to recognize specific RNA sequences.

Proteins that bind to the antibody will change the nanowire's electrical conductance and this can be measured by a detector. As a result, proteins produced by cancer cells can be detected and earlier diagnosis of tumour can be achieved<sup>23</sup> (Figure 14).

Nanoparticle contrast agents are being developed for tumor detection purposes. Labeled and non-labeled nanoparticles are already being tested as imaging agents in diagnostic procedures such as nuclear magnetic reso-



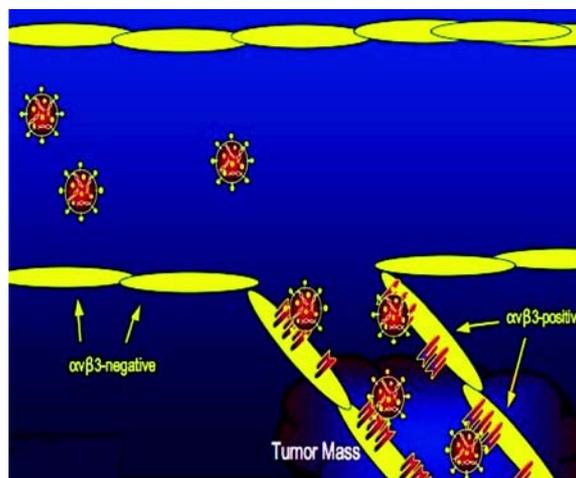
**Figure 14.** A representation that explains how nanowires can be used for detection of cancer biomarkers.

nance imaging<sup>24</sup>. Such nanoparticles are paramagnetic ones, consisting of an inorganic core of iron oxide coated or not with polymers like dextran. There are two main groups of nanoparticles: 1) superparamagnetic iron oxides whose diameter size is greater than 50 nm, 2) ultrasmall superparamagnetic iron oxides whose nanoparticles are smaller than 50nm<sup>25</sup>. Moreover, quantum dots being the nanoscale crystals of a semiconductor material such as cadmium selenide, can be used to measure levels of cancer markers such as breast cancer marker Her-2, actin, microfibril proteins and nuclear antigens<sup>26</sup>.

**Tumour treatment** can be succeeded with nanoscale devices (such as dendrimers, silica-coated micelles, ceramic nanoparticles, liposomes). These devices can serve as targeted drug-delivery vehicles capable of carrying chemotherapeutic agents or therapeutic genes into malignant cells. As an example, a nanoparticle-based drug called “*Abraxane*”, consisting of paclitaxel conjunctive to protein albumin particles, was approved by the Food and Drug Administration for breast cancer treatment a year ago<sup>27</sup>.

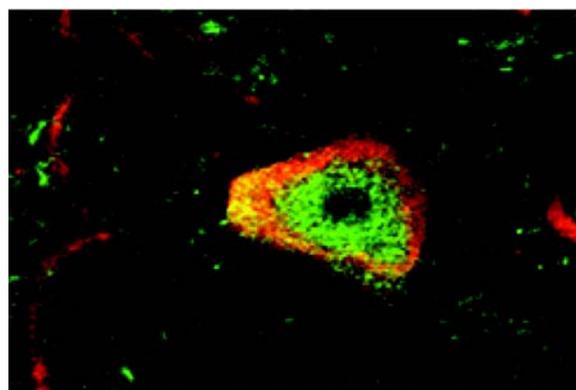
It is worthwhile to mention that selective delivery and targeting of nanoparticles to tumours may overcome the problem of toxicity and may increase the effectiveness of drug delivery. The barriers involving this procedure and that should be under consideration, are a variety of physical and anatomical characteristics of solid tumours, such as the necrotic core with the surrounding hypoxic area, the elevated local temperature and the interstitial liquid pressure. The vascular permeability of the tumour influence the retention of intravenously administered nanoparticles, and the subsequent nanoparticle drug-delivery are shown in Figure 15<sup>14,28,29</sup>.

Several approaches have been used to target nanoparticles to tumour-associated antigens, including direct conjugation of nanoparticles to monoclonal antibodies, modified plasma proteins or viral vectors. Recent progress has been made with targeted viral vectors for gene therapy applications. Figure 16 demonstrates a



**Figure 15.** Nanoparticle drug – delivery accumulation at tumour site.

nanoparticle-delivered EGFP gene (gene coding for Enhanced Green Fluorescent Protein) (green) expressed in a nerve cell (red)<sup>19</sup>.

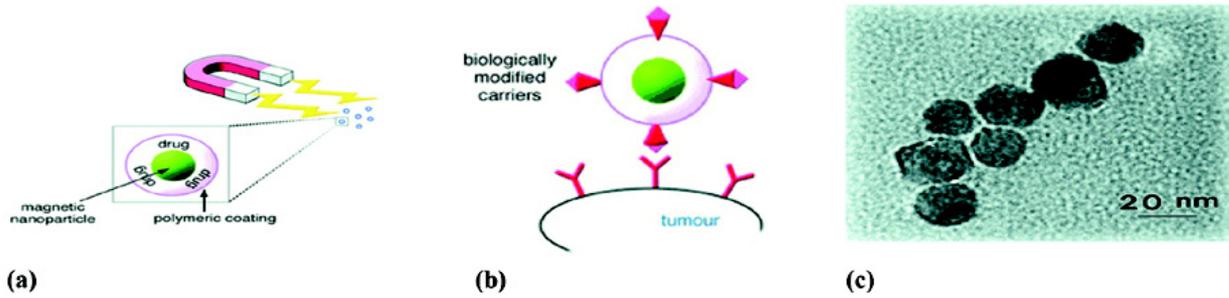


**Figure 16.** Gene therapy via nanoparticles<sup>19</sup>.

In addition to this, laser-induced thermal effects around nanoparticles, attached to specific targets have recently been used for the treatment of cancer. The basic concept for this application of Nanotechnology is the fact that nanoparticles of different properties (magnetic, optical etc.), due to their size, can be delivered more easily to target cells than can larger particles, via conjugation with antibodies, conjugation to viruses and physiological transportation as shown in Figure 17<sup>14,28-30</sup>.

After reaching target cells, these nanoparticles are then self-assembled into larger nanoclusters within cells. Afterwards, these nanoclusters can be activated by laser irradiation, microwaves or magnetic fields, depending of the nanoparticles' synthesis. By this process and its photothermal effects, destruction of cancer can be achieved.

More specifically, the nanoshell-assisted photo-thermal therapy (NAPT), is a non-invasive procedure for selective photo-thermal tumour destruction. It is based

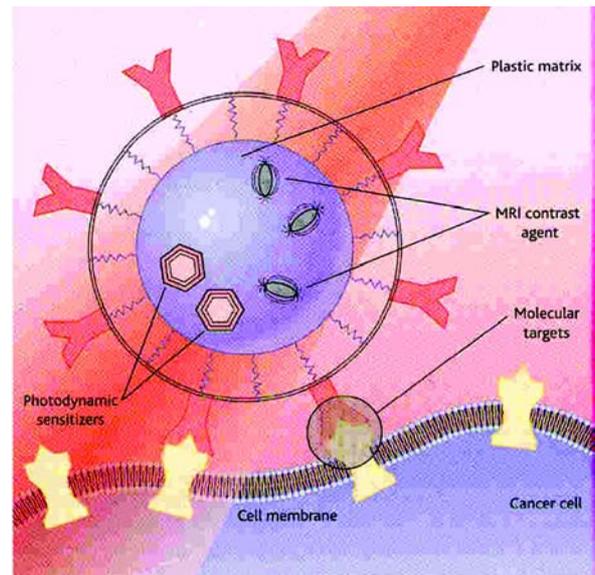


**Figure 17** a) External magnetic field-guiding the magnetic drug carriers near the tumour, b) surface antigen recognition attaching the carriers to the tumour for drug release on site, c) electron microscopy image of magnetic nanoparticles.

on nanoshells that absorb light in the near infrared (NIR) region, which is the wavelength that optimally penetrates tissues. These nanoshells have a core of silica coated with a metallic layer, usually of gold. The metal shell converts the absorbed light into heat with great efficacy. Further specificity can be engineered by attaching antigens on the nanoshells which are specifically recognized by the cancer cells. By supplying a light in NIR from a laser, the particles produce heat, which destroy the tumour. It has been found that, the temperature within the nanoshell-treated tumours rose by about 40°C compared to a rise in 10°C in tissues treated with NIR light alone. The benefit of thermal therapeutics is that most procedures are non-invasive and have the potential to treat tumours which can not be surgically treated<sup>31</sup>.

In-vivo, Raoul Kopelman, Ann Arbor and colleagues, of the University of Michigan, have recently created three-component nanoparticles that target, image and destroy tumors in the brains of rats. The particles consist of an iron oxide core that serves as a magnetic resonance imaging (MRI) contrast agent. Attached to them are copies of a cancer-targeting peptide called F3, as well as a light-absorbing compound called photofrin that kills cells when hit with red light (Figure 18). When Kopelman's team used their combination particles to treat rats previously injected with cancer cells inside their brains, animals receiving the combination particles survived more than twice as long as control animals receiving the nontargeted photofrin compound<sup>32</sup>.

**Gene-, Protein-, Lab-on-a-chip Devices, “Theranostics”:** Medical devices for in-vitro diagnostics, such as gene-, protein- or lab-on-a-chip devices, do not have any of the safety concerns associated with nanoparticles introduced into the body. Numerous devices and systems for sequencing single molecules of DNA are feasible. Nanopores are finding use as new nanoscale technology for cancer detection enabling ultrarapid and real time DNA sequencers. In general, developments in protein-chips and lab-on-a-chip devices are more challenging compared to gene-chips. These devices are anticipated to play an important role in medi-



**Figure 18** Triple threat-Multifunctional nanoparticles can combine tumor-seeking sensors, imaging agents and toxins that kill cancer cells<sup>32</sup>.

cine of the future, as they will be personalised and will combine diagnostics with therapeutics into a new emerging medical area called “theranostics”.

Over the next ten to twenty years nanotechnology may fundamentally transform science, technology, and society offering a significant opportunity to enhance human health in novel ways, especially by enabling early disease detection and diagnosis, as well as precise and effective therapy tailored to the patient<sup>2</sup>. Molecular diagnostics markets, for example, overlap with markets for non-molecular diagnostic technologies in the in-vitro diagnostic market and are less well defined than those for pharmaceuticals<sup>33</sup>.

**Prospects of Nanotechnology in Medicine and virtual Environments:** Intelligent imaging, robotics and, in particular, nanotechnology developments will have key implications for the development of future biomaterials in the following areas:

- External applied surgery will require biomaterial

properties to be controlled remotely, perhaps by self-assembly or development “in-situ”,

- Biomaterials that can be secured to anatomic structures using less invasive surgical procedures,
- Improved accuracy in the placement of biomaterial devices,
- Smart implants that react to implanted biosensor,
- Implanted biomaterials will be used to control the delivery of some drugs and biologics<sup>34</sup>.

To emphasize the expectations in nanotechnology in medicine, the results of the 7<sup>th</sup> Japanese Delphi Report and assessment of nanotechnology relevance is given in Table 2. According to this Table, there will be a widespread use of technology in the years 2010-2020, in order to elucidate, diagnose and treat several diseases, such as Alzheimer’s disease, diabetes and heart diseases.

Finally, applications of special relevance to improving health and enhancing human physical abilities include the use of virtual environments for training, education, and interactive teaching. This will provide new ways for medical students to visualize, touch, enter, smell, and hear the human anatomy, physiological functions, and medical procedures, as if they were either the physician or a microscopic blood cell traveling through the body. Similarly, impaired users, ordinary people, athletic coaches, and a range of health-related professionals could train in these virtual environments.

## 5. Possible Risks for Human Health and Ethical

### Questions

While products based on nanotechnology are actu-

ally reaching the market, sufficient knowledge on the associated toxicological risks is still lacking. The literature on toxicological risks of the application of nanotechnology in medical technology is scarce.

Reducing the size of structures to nanolevel results in distinctly different properties. As well as the chemical composition, which largely dictates the intrinsic toxic properties, very small size appears to be a dominant indicator for drastic or toxic effects of particles. It is generally accepted that nanoparticles pose a separate problem within the area of toxicology, designated as nanotoxicology. Therefore, chemicals and materials in nanoformulation need to be evaluated for their activity and toxicity as nanoparticles. Chemical composition, which dictates the intrinsic toxic properties of the chemical is of significant importance in determining the toxicity of particles.

It has been found that biodegradable substances are normally decomposed and their waste products excreted by the kidneys and intestines<sup>27</sup>. However, non-biodegradable nanoparticles have been studied and it seems that they accumulate in certain organs, especially to the liver. It is not clarified the potential harm they may trigger, or at what dosage, but further investigation is needed<sup>35</sup>.

Based on these conclusions, the development of specific guidance documents at a European level for the safety evaluation of nanotechnology products applied in medical technology is strongly recommended and the need for further research in the field of nanotoxicology is clearly identified.

Ethical and moral concerns also need to be ad-

**Table 2.** Expectations of nanotechnology applications in medicine and realization time<sup>34</sup>.

Expectations of Nanotechnology in Medicine	Year
• Widespread use of palliative care in the final stage of life of elderly people, of scientific guidelines for lifestyles (nutrition, rest and exercise) to prevent lifestyle-related diseases	2010
• Widespread use of a system in which all medical data of an individual, such as test results, medical history, and prescribed medications, are stored on a single card	2011
• Widespread use of non-invasive diagnosing methods to determine the level and extent of arteriosclerosis	2012
• Elucidation of the arteriosclerosis contraction mechanisms	2013
• Elucidation of carcinogenic mutation mechanisms, of cancer metastasis mechanisms, of the contracting mechanisms in Alzheimer’s disease	
• Widespread use of drugs to cure viral liver disease, Widespread use of an oral insulin treatment method	2014
• Development of a cell therapy method for myocardial infarction	2015
• Widespread use of early diagnosis methods based on blood tests for almost all cancers	
• Development of treatment methods capable of completely curing allergies such as atopic dermatitis	2016
• Early elucidation of the appearance of unknown virulent pathogens through a global surveillance system to prevent their world-wide spread	
• Practical use of effective methods against cancer metastasis	
• Widespread use of methods to prevent cancer based on genetic diagnosis	2017
• Improvement in the average five-year survival rate for all types of cancer to more than 70%	2020
• Widespread use of regenerative treatment technology for damaged organs using embryonic stem cells, of treatment methods capable of completely curing Alzheimer’s disease	
• Elucidation of individual aging mechanisms	2021

dressed in parallel with the new developments in some areas, for example, neuroethics need to be investigated before brain and neural system research. Another key challenge is forecasting and addressing possible unexpected ethical, environmental and health consequences of the revolutionary science and engineering developments in nanobiosystems. Priority science and technology goals may be envisioned for international collaboration in nanoscale research and education: better comprehension of nature, increasing productivity, sustainable development and improving human performance<sup>36</sup>.

### Conclusions

Nanotechnology in modern medicine and nanomedicine is in infancy, having the potential to change medical research dramatically in the 21<sup>st</sup> century. Nanomedical devices can be applied for analytical, imaging, detection, diagnostic and therapeutic purposes and procedures, such as targeting cancer, drug delivery, improving cell-material interactions, scaffolds for tissue engineering, and gene delivery systems, and provide innovative opportunities in the fight against incurable diseases. Thanks to nanotechnology tools and techniques, there has been a huge progress on understanding the function of biological structures and their interaction and integration with several non-living systems, but there are still open issues to be answered, mainly related to biocompatibility of the materials and devices which are introduced into the body. Many novel nanoparticles and nanodevices are expected to be used, with an enormous positive impact on human health. The vision is to improve health by enhancing the efficacy and safety of nanosystems and nanodevices. In addition, early diagnosis, implants with improved properties, cancer treatment and minimum invasive treatments for heart disease, diabetes and other diseases are anticipated. In the coming years, nanotechnology will play a key role in the medicine of tomorrow providing revolutionary opportunities for early disease detection, diagnostic and therapeutic procedures to improving health and enhancing human physical abilities, and enabling precise and effective therapy tailored to the patient.

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