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Nanomedicine in Cancer

César A González

Universidad del Ejército y Fuerza Aérea

Instituto Politécnico Nacional

México

1. Introduction

Nanotechnology is now a very important field of study in most academic institutions around the world. The industry has concentrated its efforts on nanotechnology as it has shown that investment in this field is very profitable. The development of research in the area of nanotechnology requires sophisticated equipment and techniques including: scanning electron microscopy, transmission microscopy with accessories to achieve high resolution, quantum tunneling microscopy, X-ray spectroscopy of dispersion energy, as well as electron diffraction of low energy.

The use of nanotechnology suggests that certain fields of medicine can be a revolution, specially in monitoring the disease through imaging, tissue repair, and control of the evolution of diseases, protection and improvement of biological human systems, pain relief and administration of drugs to specific cells, just to refer some of the most important applications. All these applications would be new technological advances that are promoting a new era in assistencial medicine.

Cancer is a leading cause of death throughout the world. Of the 58 million deaths that occurred in the world in 2005, 7.6 million (13%) were due to cancer. The types of cancer leading to overall mortality in humans are the lung, stomach, liver, colon and breast. Over 70% of all cancer deaths occurred in developing countries. It is expected that the global number of deaths from cancer continue to increase throughout the world and reach 9 million in 2015 and 11.4 million in 2030.

Nanomedicine has shown an important growing in the war against cancer in the last two decades. Early detection is the main limitation of the current cancer treatments. Several techniques at molecular scale have been focused on early detection and treatment of the disease by identification and selective targeted of cancer cells but their applications in the clinical practice still represent important methodological challenges. The National Cancer Institute of the United States has launched the "Alliance for Nanotechnology in Cancer", a plan that includes the development and creation of miniature tools for early detection and effective treatment of this evil affects millions of people in the world.

It is currently designing new nanoscale devices, i.e. nanodevices capable of one or more clinical features, including the detection of cancer in its earliest stages, tracking their location inside the body, or the supply of drugs specifically targeting malignant cells. This chapter is oriented to describe newer nanodevices designed to detect cancer in early stages as well as its specific location in the body. The information is presented as a contrast between the innovative value of the concept and their clinical feasibility. The main body of the content is segmented as follows: First; new nanostructures for labelling cancer cells are cited. Second; image techniques for cancer detection assisted by nanostructures are roughly reviewed. Then; an author proposal for cancer detection and monitoring through magnetic fields at multiple frequencies assisted by magnetic nanoparticles is described, including its theoretical and practical fundamentals. Last; potential hazards of nanomedicine in cancer are briefly described.

2. Nanostructures for Labelling Cancer Cells

The research in nanotechnology that is focuses on the diagnosis of cancer is currently considered in two main fronts: diagnostic based on laboratory and *in vivo*. This section present some representative nanostructures currently designed for labelling tumoral cells and its implication in the cancer diagnosis at both laboratory and *in vivo* levels.

The "nanowires" are 1-20 nm nanostructures constructed trough an array in which the silicon is coated with antibodies (bioreactivas molecules) that recognize tumor cells. The coupling of "nanowires" to regions of tissue with tumor cells produce a change in the electrical conductivity of the tissue that can be detected and measured using electronic instrumentation, which indicates the presence of a tumour in the body, the sensitivity could be up to 100 times greater than other diagnostic techniques based on normal imaging (Benerjee and Verma, 2006).

The "cantilevers" or flexible nanorods are constructed using lithographic techniques used in the semiconductor industry. These devices are formed with nanorods covered with molecules capable of binding to specific substrates such as DNA (Deoxyribonucleic Acid) or antibodies directed to a genetic sequence from tumour cells, thus allowing timely diagnosis of cancer in patients (Ziegler, 2004).

Currently have been developed a wide variety of nanoscale particles (20-400 nm) that serve as devices for the diagnosis of cancer, i.e. superparamagnetic metal nanoparticles coupled to an antibody that has the potential to serve as nanobiomarkers, useful to detect virtually any protein or nucleic acid of tumor origin, since they are produced in excess by the cell affected, this technique add much higher detection sensitivity compared with current conventional methods (Jain et al. 2005) and (Ivkov et al. 2005).

The "quantums dots" are nanocrystals of semiconductor materials such as cadmium selenium which promise to perform the diagnoses of cancer in the laboratory. The nanocrystals are coupled to specific particles and act as sources of light whose colors are dependent on the molecular size of the particle. When "quantums dots" are attached to an antibody or another molecule able to bind to a tumour protein of interest, they act as a

beacon that emits light when it is coupled to an organ or tissue affected, allowing the diagnosis of cancer at early stages and with a high specificity (Tada et al. 2007).

One of the lines of development in nanomedicine is the "nanotubes", which are composed of lamellar or spherical structures of carbon atoms. These are known as bio-carriers nanodevices, which can transport drugs or molecules such as proteins or DNA directly to inside of tumour cells to be used as nanobomb, which will pop by stimuli such as light and infrared light to destroy tumour cells without affect normal cells (Kam et al. 2005).

The potential use of nanoparticles to modulate the gene expression has been recently shown; targeted human serum albumin nanoparticles loaded with antisense oligonucleotides against polo-like kinase 1 (Plk1) were developed. The coupling of the antibody trastuzumab to nanoparticles showed a specific targeting to HER2-overexpressing BT-474 cells. Authors observed a reduction of Plk1 mRNA and protein expression as well as an increased activation of Caspase 3/7. The study provides the basis of an alternative technique for tumour treatment promoting a better agents penetration into primary and metastatic target cells (Spänkuch, 2008).

Recently; some innovative groups are in the process of creating prototypes of next-generation nanodevices called "Nanobots" or nanorobots. It is intended that the nanorobots will be designed as nanostructures with 200 to 600 nm with features of auto replication and total autonomy. An example of this technology is the vehicle anti-cancer developed in the European community, which can carry anti-cancer drugs and directed specifically towards the site where the tumour, and once located the target, release a regulated drug that selectively destroy tumor cells without affecting other normal cells.

3. Image Techniques for Cancer Detection Assisted by Nanostructures

3.1 Current systems for cancer diagnosis and its limitations

Magnetic Resonance Imaging (MRI) systems provide the advantage of high spatial resolution in very well differentiated pathological tissue, in contrast; MRI shows a poor spatial differentiation of neoplasies in early stages as well as disseminated cancer during metastatic processes, and is necessary to increase the spatial resolution of the MRI systems in order to get a useful diagnosis. Other method to get images related to the diagnosis of neoplasies is the Computerized Tomography (CT). CT uses the basic principles of the conventional radiography (X-ray) to create a map of the tissue in a specific region, limitations about spatial resolution for cancer detection are similar than those reported for (MRI). Different image techniques by contrast agents have increased the resolution of MRI and CT systems; nevertheless a poor specificity still represents a technical limitation.

Tumour associated to cancer is visible on both MRI and CT. However, the diagnostic is complicated by the fact that on CT it produces low signal, which can be confused with low-signal producing edema. On MRI tumours produces a hypersignal, which may be confused with hypersignal producing edematous tissue. Specific detection and continuous monitoring of edema differenced of tumours is also important in treatment and assessment of medical condition. The technical characteristics of MRI and CT equipments, as well as the difficulties

to transport and maintain patients in the MRI and CT physical spaces convert those systems as unviable equipments for continuous monitoring of the critically ill in intensive cares and emergency rooms.

It is well reported that the hypervascularisation of malignant neoplasies promotes changes in the Electrical Impedance (EI) of tissue, this conditions have suggested the use of bioimpedance measurements to detect cancer in different organ and tissues. Scharfetter and colleagues have considered the Electrical Impedance Spectroscopy (IES) as a possibility to produce information relative to abnormal conditions in tissues (Scharfetter, 1999). Some researchers as Newell and Holder have proposed the use of Electrical Impedance Tomography (EIT) as an important method to evaluate and monitor neoplasies in different organs and tissues (Newell, 1996), (Holder, 1999). EIT uses an arrangement of electrodes to inject subsensorial currents and measure the resultant voltages. Data are used to reconstruct a map of the tissue impedance. Griffiths proposed the use of bioelectrical measurements by non-invasive electromagnetic coils as a valuable alternative to monitor, without physical contact, the health status of organs and tissues (Griffiths et al., 1999) and (Griffiths, 2001). Several authors as Al-Zeiback and Korzhenevskii have concurred in the proposal of non-contact measurements for the development of alternative imaging techniques by Magnetic Induction Tomography (MIT) (Al-Zeiback et al. 1993), (Korzhenevski and Cherepenin, 1997) and (Korjnevsky and Cherepenin, 1999).

The sensibility of EIT and MIT is a function of the electrical properties of the studied organ or tissue, and the electrical conductivity provides an important contribution. The main EIT and MIT application have been focused on the detection of edema (fluid accumulation). The use of bioimpedance measurements in the detection of malignant tumors still represents a technological challenge because the electrical conductivity of tumoural tissue is poorly differentiable with respect to normal tissue. In study reported by Burdette, normal and tumoural human mama tissue represent electrical conductivities of 4 and 3.5 to 8 mS*cm⁻¹ respectively, both measured at 500MHz (Burdette, 1982).

3.2 Bioconjugated nanoparticles in cancer diagnosis and its limitations

Monoclonal antibodies allow the typification of tumoural cells by specific antigens recognition (bioreactive molecules in the cell's surface). Currently is possible to develop the union of different monoclonal antibodies to magnetic nanoparticles, those nanoparticles have a preconditionated surface for the union of bioreactive molecules such as proteins or antibodies. DeNardo developed a method to design reactive bio-probes, which allow the coupling of the complex antibody-nanoparticle to the membrane of tumoural cells. Experimental results have shown the specificity of such probes when are in contact with tumoural antigens (DeNardo et al. 2005).

Some researchers e.g. Magin and Saini have developed effective contrast agents to MRI and CT based on the use of magnetic and supermagnetic nanoparticles (Magin et al. 1986) and (Saini et al. 1987). As Ito et al. explain; the objective to use those characteristic nanoparticles has been to improve the contrast between tissues decreasing the relaxation signal T2 for the case of MRI (Ito et al. 2005). The results indicate that such methods have

technical viability; however its potential application in the clinical practice demands the use of expensive and complex imaging systems available in few medical facilities.

Shinkai et al. proposed the use of an impedance magnetic sensor for malignant tumor diagnosis in brain assisted by magnetic nanoparticles. The proposed diagnosis technique involves nanoparticles magnetization by a static magnetic field of 1.8T (Shinkai et al. 1998). The nanoparticles magnetic field distribution is detected by the impedance magnetic sensor with high resolution for static magnetic fields; the spatial resolution of the system is a function of the magnetization field intensity; which demands energy, large and impractical magnets as portable systems for continuous monitoring.

Current in vivo cancer diagnosis in organ and tissues based on contrast imaging techniques assisted by magnetic nanoparticles depend on the use of systems with complex and expensive technology which are available to only a small part of the prospective patient population in danger of developing cancer; therefore the whole concept of imaging assisted by nanotechnology still represents technical challenges before to be considered a portable tool for non invasive cancer diagnosis and continuous monitoring of the therapeutic response in oncology departments, rural population and medically underserved populations.

4. Magnetic Induction Spectroscopy (MIS) for Cancer Detection

The use of MIS (magnetic fields at multiple frequencies) assisted by magnetic nanoparticles has been proposed as a non invasive and inexpensive technique for cancer detection. To this end the author of this chapter has suggested that measuring induction phase shift throughout the bulk of tumoural tissue in time and over a broad range of frequencies, instead of producing an image of the tumor, could be used as an inexpensive and mobile alternative technique for cancer detection. The method includes the union of magnetic nanoparticles coupled to target cancer cells, and the effect produced by that coupling in the spectrum of inductive phase shift at multiple frequencies. The principle is based on the use of a primary magnetic field which induce a current density in tissue, those currents generate a second magnetic field which perturb the primary magnetic field, the magnitude of the perturbation is a function of the tissue electrical properties, mainly because the electrical conductivity. Selective coupling of magnetic nanoparticles to tumoural cells in a specific tissue volume increases the volumetric tissue electrical conductivity; in consequence an increase of the primary magnetic field perturbation is observed. The perturbation could be measured as a spectrum of phase shift in a second sensor coil. The magnitude and morphology of the inductive phase shift spectra determine the presence of tumoural tissue, metastatic processes and in general cancer in organ and tissues.

In order to optimize the detection technology, in recent study has been explored the possible use of a magnetron coil on the inductive volumetric phase shift of the brain in the presence of a haematoma (González et al 2007). The sensitivity of a magnetron coil with that of a circular coil has been compared. The results have shown that the magnetron coil has a somewhat greater sensitivity to the detection of a haematoma than the circular coil (González et al 2007). The effect of haematoma location in the brain on the planar magnetron

and circular coil measurement, with a numerical simulation has been explored. The results reveal that the location of the haematoma has a substantial effect on the sensitivity of the magnetron and circular coils. Furthermore, we find that at certain different frequencies the various locations of the haematomas produce no volumetric phase shift. (Rojas et al 2008). Those changes in the spectra of inductive phase shift are expected to be amplified by the use of magnetic nanoparticles coupled to tumoural cells.

4.1 Theoretical fundamentals of MIS assisted by magnetic nanostructures

i. Selective coupling of bioconjugated nanoparticles

The selective coupling principle of bioconjugated nanoparticles to tumoural cells is based on the union of magnetic nanoparticles to molecular ligands with affinity to specific bioreceptors in tumoural cells. Specifically the covalent union of magnetic nanoparticles to monoclonal antibodies (bioconjugated nanoparticle-antibody) has been proposed as cancer markers. To create bioconjugated nanostructures the use of magnetic nanoparticles with magnetite nucleus (Fe_3O_4) and polisaccharide coat with functional carboxyl groups has been chosen. The typical diameters are in the order of 50 to 300 nm and have superparamagnetic properties. The ligand of the bioconjugated corresponds to monoclonal antibodies with amino functional groups activated by carbodimine. Carbodimine reacts with carboxyl groups of the magnetic nanoparticles to produce O-acilurea and amino ligand reactions. These reactions produce a covalent union that warrants a stable coupling of the magnetic nanoparticle to the antibody. Figure 1 shows schematically a representation of the principle of the covalent union by carboxyl groups of magnetic nanoparticles and its ligand given by a monoclonal antibody. The bioconjugated nanoparticle-antibody is added to the cell membrane by a non-covalent union created between the antibody and its receptor (biomarker) in the cell surface.

ii. Increment of the electrical conductivity in tumoural tissue

Different electrical circuits have been proposed to represent the electrical behaviour of cellular suspension and biological tissues as a function of its electrical properties. (Schwan, 1957), (Tregear, 1966) and (Salter, 1979). Cole and Cole proposed a general electric circuit to represent biological materials as a function of its electrical properties and frequency. Their model suggests the representation of membrane cells as capacitive elements, as well as the protein structures, intracellular and extracellular fluids as resistive elements. The simplified equivalent circuit suggests a parallel-series resistive-capacitive arrangement. The composed electrical conductivity of such model is a function of the permittivity of the membrane cell, protein content, intracellular fluids and frequency; those factors are reflected as changes in the electrical conductivity. The mathematical expression to estimate the composite electrical conductivity is given by eq. (1) (Cole and Cole, 1941), (Cole and Cole, 1942).

$$\sigma = \sigma_0 + \frac{\Delta\sigma}{1 + (j\omega\tau)^{-\alpha}} \quad (1)$$

Where σ_0 represents the electrical conductivity of the material in direct current, $\Delta\sigma$ corresponds to the changes in electrical conductivity which could be associated to the presence of magnetic nanoparticles, ω is the angular frequency, τ is a temporal constant

corresponding to the arrangement resistive-capacitive and α represents positive values $1 \geq \alpha \geq 0$.

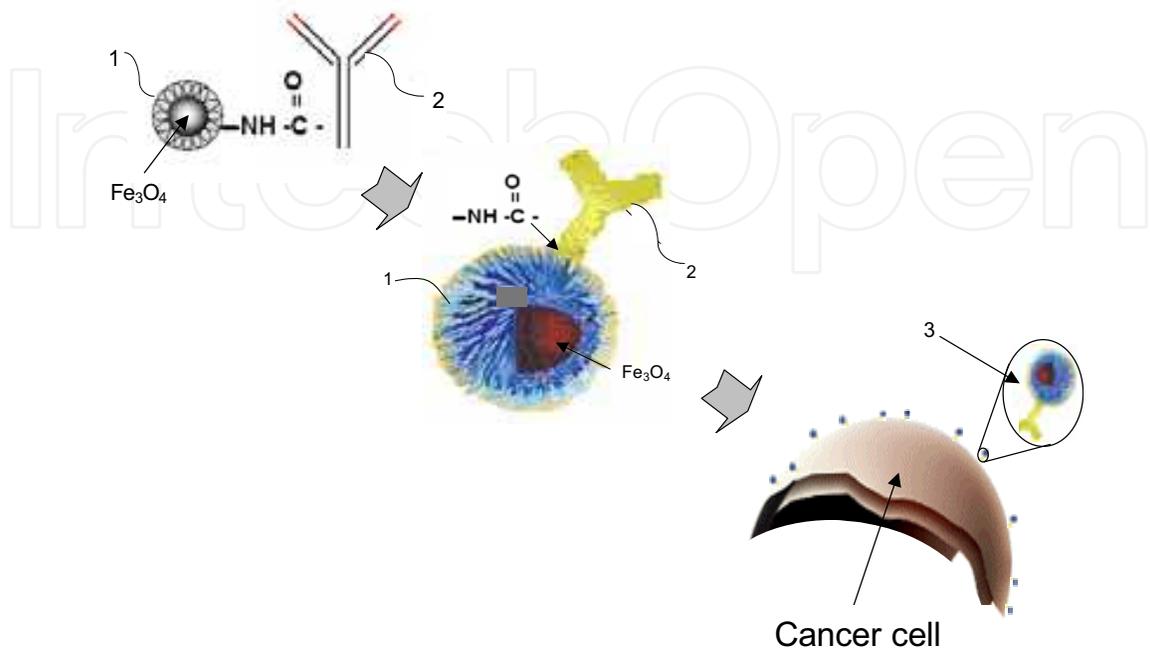


Fig. 1. Representation of the principle of a covalent union between carboxyl groups (1) of the coat of magnetic nanoparticles (Fe_3O_4) and specific ligand of cancer cells given by a monoclonal antibody (2). The structure conformed is known as bioconjugated "nanoparticle-antibody" (3).

iii. *The effect of electrical conductivity changes in tumoural detection by MIS*

Currents induction in conductive materials by oscillating magnetic fields is explained in the basis of the Faraday induction law; which formulated in terms of the Maxwell general equations is expressed by:

$$\Delta \times E = -\partial B / \partial t \quad (2)$$

Eq. (2) indicates that a variable magnetic field \mathbf{B} induces an electromotive potential \mathbf{E} in a conductive media, such potential is a function of the magnetic flux and induces an electrical current flux in the medium, those currents are known as eddy currents.

Accordingly with the charge conservation law, an induced current density \mathbf{J} in a conductive material is directly proportional to the induced electrical potential \mathbf{E} and to the electrical conductivity σ of the material. The charge conservation law derived from the Maxwell general equations is formulated as:

$$J = \sigma E \quad (3)$$

Eq. (3) allows to argue that and increase in the electrical conductivity represents an increase of the energy absorbed by the material; then the union of bioconjugated magnetic

nanoparticles to the membrane cells through selective monoclonal antibodies promotes that the electrical properties of tumoral cells change in such a way that increments in the composite electrical conductivity are observed. Those conductive increments allow that magnetic fields of different frequencies induce eddy currents selectively in the marked tumoural cells, then the perturbations of the magnetic fields are larger than those generated in healthy tissue; it means those generated without the union of magnetic nanoparticles to the membrane cells.

4.2 Practical description of how to detect cancer in vivo by MIS

In vitro cancer detection represents a promising concept for non-invasive diagnosis and monitoring. Figure 2 shows the basic concept for tumoural cells detection in suspension through the use of MIS assisted by magnetic nanoparticles. The assumption is early cancer detection in blood through magnetic nanoparticles coupled to specific tumoural biomarkers (i.e. Her2/neu, +hMAM or +Survivin) that are overexpressed in blood cells at the first stages of cancer. The volumetric electrical conductivity increments of tumoural cells given by the presence of magnetic nanoparticles promote increments in the perturbation of the MIS fields and the inductive phase shift spectrum.

Cancer detection by MIS at an organ or biological tissue comprising: a body or volume of biological tissue exposed to the in vivo interaction with bioconjugated magnetic nanoparticles, such organ or volume of biological tissue is positioned between a first antenna or inductive coil and a second antenna or detector coil, an injection spectrum of current variable in a wide bandwidth in the first coil or antenna, detecting the spectrum of voltage variable induced in the second coil or antenna, an estimation of the spectrum of inductive phase shift between the first and second coil or antenna, and depending on the morphological characteristics and magnitude of the spectrum of inductive phase shift detected, it could be associated to the presence of cancer cells, malignant tumours or metastases in the volume under study.

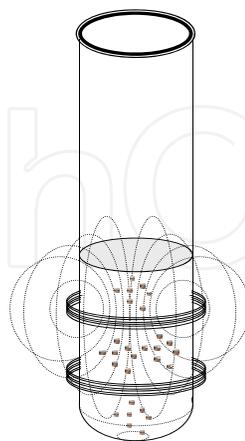


Fig. 2. Basic concept for tumoural cells detection in suspension through the use of MIS assisted by magnetic nanoparticles. The concept is early cancer detection in blood through magnetic nanoparticles coupled to specific tumoural biomarkers that are overexpressed in blood cells at the first stages of cancer.

The *in vivo* interaction of the organ or volume of biological tissue being studied with bioconjugated magnetic nanoparticles is developed through the intravenous infusion of magnetic nanoparticles coupled to a monoclonal antibody which is characteristic of specific receptors overexpressed on the surface of target cancer cells. Figure 3 shows a general scheme about how to detect breast cancer *in vivo* by MIS. First; the bioconjugated nanoparticle-antibody is injected intravenously to reach the tumoural region increasing its electrical conductivity. Then; increments in the inductive phase shift associated to the presence of tumoural cells or metastatic processes are detected by MIS. The idea is to take advantage of the condition in which the electrical conductivity of the tumour is increased to amplify the magnitude of the inductive phase shift spectrum.

A general description of the electronic instrumentation involves the generation of magnetic fields through a programmable digital synthesizer connected to the first coil. The collection of signals in both coils is via a differential amplifier, the phase difference signal between the two coils is estimated through a phase detector circuit. A control system programming is done through an analog-digital converter and a dedicated microprocessor. In general; the technological proposal is a minimally invasive method for the detection of malignant tumours and metastatic processes in organs and tissues.

5. Hazards of Nanomedicine in Cancer

Nanomaterials have a unique surface contact layer with the body tissue in comparison to bulk materials, and this unique property needs to be investigated from a toxicological point of view. Given the unique reactive characteristic of nanoparticles; it's expected that nanoparticles have an impact on the toxicity but it may differ depending on the type of particles used (i.e. biological vs non-biological origin). Nanoparticles have different physico-chemical characteristics in comparison to microsize particles, those typical characteristics may result in different distributions of the particles inside the body as well as side effects. In this sense; it is expected that the nanostructural interaction in tissues and cells, as well as its potential toxicity, greatly depend on the composition of the nanoparticle.

Magnetic iron oxide nanoparticles have been used intravenously as MRI contrast fluids in the clinical practice of cancer detection; the body distribution profile of those nanoparticles has been shown to depend on size, charge and thickness of the coating (such as dextran-coating) of the nanoparticles [Chouly et al, 1996]. In addition; it has shown that new magnetic contrast agents could be compartmentalised in lysosomes, exocytosed and returned to the normal iron pool. Nanoparticle degradation was shown to be dependent on coatings more than on particle sizes [Briley Saebo, 2004]. The key safety issue with these products in the clinical practice is the risk of anaphylactic reactions. In recent review about toxicology of nanoparticles used in health care products; is concluded that no deaths associated to nanosized magnetic iron oxide products had been reported [Costigan, 2006]. This report compared reactions to those reported for non-nanosized iron oxide intravenous therapeutic products as well as literature reports, and concluded that it is unclear whether the anaphylactic reactions are due to direct mediator releasing effects of iron (or dextran) or an immunological mediated mechanism. In addition; the study concludes that the toxicity information available regarding healthcare nanoparticles is limited. However, there were

not identified mechanisms of toxicity that would evade conventional hazard identification testing currently required [Costigan, 2006].

In general; the nanoparticles size opens the potential for crossing the various biological barriers within the body. In the best of the cases the potential to cross the blood brain barrier may open new ways for drug delivery into the brain. The nanosize also allows for access into the cell and various cellular compartments including the nucleus. Recently; De Jong and Borm have reviewed the main application and hazards of drug delivery and nanoparticles (De Jong and Borm, 2008), their main conclusion besides the potential beneficial use is drawn to the questions how we should proceed with the safety evaluation of the nanoparticle formulations for drug delivery. In view of these specificities; investigations in pharmaco-kinetic and toxicological distribution studies of nanoparticles are warranted.

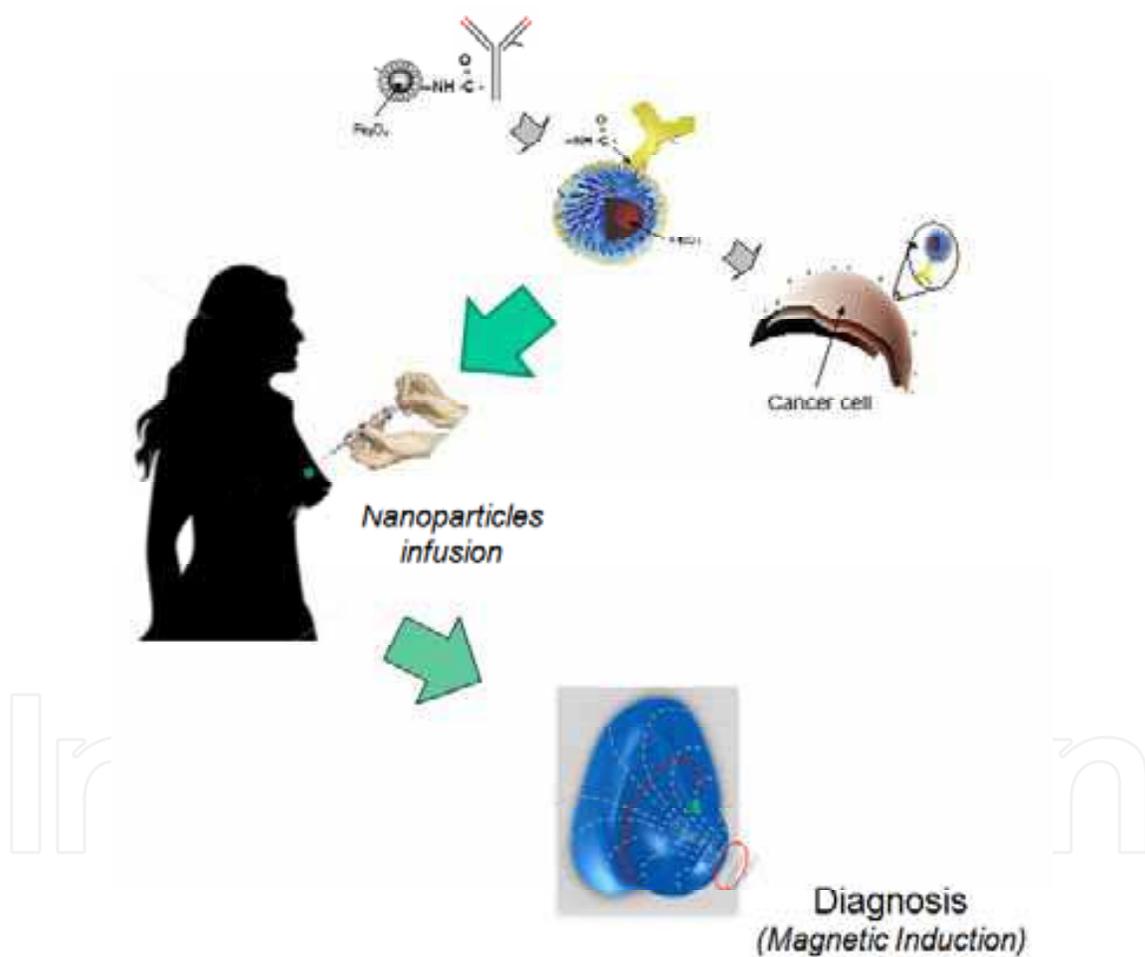


Fig. 3. General scheme to detect breast cancer in vivo by MIS assisted with magnetic nanoparticles. The bioconjugated nanoparticle-antibody is injected intravenously to reach target cells in the suspicious tumoural region and to increase its electrical conductivity. Increments in the inductive phase shift spectrum detected by MIS could be associated to the presence of tumoural cells or metastatic processes.

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Biomedical Engineering can be seen as a mix of Medicine, Engineering and Science. In fact, this is a natural connection, as the most complicated engineering masterpiece is the human body. And it is exactly to help our “body machine” that Biomedical Engineering has its niche. This book brings the state-of-the-art of some of the most important current research related to Biomedical Engineering. I am very honored to be editing such a valuable book, which has contributions of a selected group of researchers describing the best of their work. Through its 36 chapters, the reader will have access to works related to ECG, image processing, sensors, artificial intelligence, and several other exciting fields.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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