Chapter 1

Use of functional metalic nanostructures in biosensors

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1. Introduction

Nanotechnology is the scientific area which includes materials with at least one dimension smaller than 100 nm. Not only the size but also the functionality at nano or macroscale is essential for a material to be considered as nanomaterial. Beyond the vastly increasing application areas, nanostructures are becoming superstars of analytical chemistry centered research, which are devoted to nanotechnology in order to achieve higher sensitivity, lower the price and detection limits (Jianrong, Yuqing, Nongyue, Xiaohua & Sijiao, 2004; Merkoçi, 2013). The integration of nanomaterials into biosensing systems represents one of the hottest topics of the todays research. Science direct search for the keywords "Nanomaterial AND Biosensor" came up with 1380 article and 138 reviews in Chemistry, Analytical Chemistry and Material Science Journals in the last five years, with a logarithmic increase in report number per year. This increased demand is due to unique properties possessed by nanoscale materials as a result of their tailorable nanosize and structure which offer excellent prospects for designing novel sensing systems and enhancing the performance of the biorecognition element with proved electronic signal transduction (Jianrong et al., 2004; Merkoçi, 2009).

The engagement of nanomaterials with sensing devices and/or in building sensor platforms generates novel interfaces that enable optical or electrochemical detection of the biomolecule of whim with enhanced sensitivity (Jianrong et al., 2004; Michalet, Pinaud, Bentolila, Tsay, Doose, Li et al., 2005; Putzbach & Ronkainen, 2013). Nanomaterial can enrolled as either effective optical (Byun, 2010) (Staleva, Skrabalak, Carey, Kosel, Xia, Hartland et al., 2009), fluorescent (Michalet et al., 2005), and catalytic labels (Saha, Agasti, Kim, Li & Rotello, 2012) (Costa, De la Escosura-Muñiz & Merkoçi, 2010) with signal amplifying features to increase the sensor sensitivity. In the meantime, they could be functional building blocks for functional, highly catalytic and conductive sensor platforms (Zhang, Carr & Alocilja, 2009).

The number of different type of nanostructures is increasing and wide range of nanoscale materials of different sizes, shapes and compositions are now available (Burda, Chen, Narayanan & El-Sayed, 2005; Kim, Hiraiwa, Lee & Lee, 2013; Xia & Lim, 2010). From those, mainly, nanomaterials can be divided into three main classes depending on the material they are made up of: i) inorganic nanoparticles where the core material is an inorganic element or mixture (e.g; gold, silver, TiO_2, ZnO, CdS and so on) (Lee, Sung & Park, 2011), ii) organic soft nanomaterials which are formed of organic materials including lipids, peptides, genetic material, (Genç, Ortiz & O'Sullivan, 2009; Hartgerink, Beniash & Stupp, 2001) and finally, iii) nanocomposites which are based on both organic and inorganic materials, for example, magnetosomes (Goldhawk, Rohani, Sengupta, Gelman & Prato, 2012), metal coated carbon nanotubes (Jiang, Zhang, Wang, Xu & Li, 2011) and peptide amphiphiles (Templates, 2002). However, this chapter will only cover the state of the art associated to the advantages offered by different types of inorganic nanomaterials and their composites. Collection of literature on challenges and drawbacks, and real world applications of these kinds of nanomaterials in biosensor development, including current status and future prospects will also be served to the readers' interest.

2. Inorganic Nanostructures

2.1. Gold and Silver nanoparticles

Gold and silver are the most widely employed metals in nanotechnology, which their use goes back to ancient times (e.g. for staining ruby glass (Himmelhaus & Takei, 2000), potion making, as healer (Vohs & Fahlman, 2007), bactericide (Matsumura, Yoshikata, Kunisaki & Tsuchido, 2003) and medicine (Mahdihassan, 1984)). Today, scientific authorities have also appreciated gold and silver due to their size and shape depended unique optical, electrochemical and electrical properties which can be altered towards the needs of specific applications including targeted drug therapy (Wang, Sui & Fan, 2010) and design of diagnosis and screening tools (Esseghaier, Ng & Zourob, 2012). In particular, these nanoparticles have great potential as contrast agents, fluorescent labels, and functional sensing platforms for the optical imaging and biosensing (Guo & Wang, 2007; Merkoçi, 2009, 2013).

The nanosized gold and silver show a localized surface plasmon resonance (SPR) property, which makes them perfect tools for optical sensing (D'Agata & Spoto, 2013). This size and shape depended physical plasmonic phenomenon can be explained as the absorption of the light in the visible spectrum due to the photoexcitation driven oscillation of conduction electrons inside the metal nanostructure (Mody, Siwale, Singh & Mody, 2010). A complete theoretical insight to the phenomenon was given in the book edited by Merkoçi (Merkoçi, 2013) and some other comprehensible reviews (Sato, Hosokawa & Maeda, 2007; Guerrini & Graham, 2012; Saha et al., 2012; Staleva et al., 2009; West & Halas, 2003).

The strong change in the absorption spectrum of the colloidal solution of metal nanostructures with varied sizes and shapes can be distinguishable even by naked eye. Beside these, the location of the SPR band is strongly sensitive to the environment of the nanostructure (Burda et al., 2005). A small change on the surface chemistry as a result of interaction with the target molecule will result in a strong absorbance shift from red to blue, which can easily be detected by optical methods. There are several attempts in the literature reporting optical detection of disease markers in which the detection sensitivity was altered by changing the morphology and the size of metal nanostructures, or combining with other strategies (Byun, 2010; Kim, Yoo, Park, Yoshikawa, Tamiya, Park et al., 2011; West & Halas, 2003). However, we will limit the discussion to recent examples of such achievements.

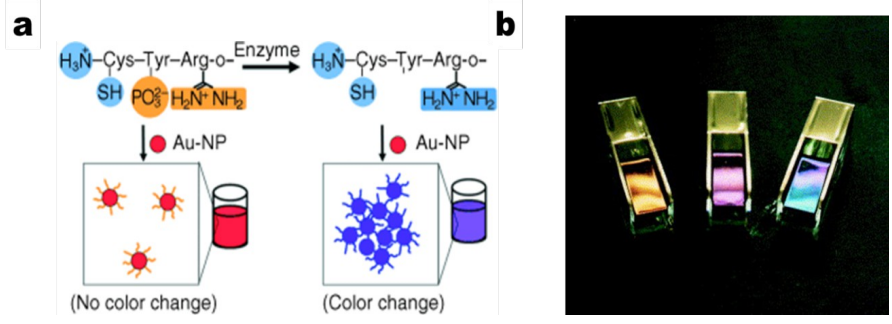

Figure 1. Gold nanoparticle based optical biosensors. a) Solution based Alkaline phosphatase (ALP) assay depicting color changes during peptide-induced Au-NP aggregation. b) Optical solid surface biosensor: cap shaped gold nanoparticles are deposited on polystyrene surface. Images are modified from Choi, Ho and Tung, 2007; Himmelhaus and Takei, 2000.

The most common strategy is the use of colloidal solution of nanoparticles which are previously bioconjugated with the capture molecule (single strand DNA, antibody/antigen, receptor, peptide and aptamer vs.) (Sato et al., 2007; Saha et al., 2012; Zhang, Guo & Cui, 2009). Interaction of the analyte with the particle surface will eventually lead a shift in SPR band which later be correlated with the analyte concentration (Figure 1a). However, the smallest working volume is limited to as much as hundreds of microns and the sensitivity of this bulk system is still poor. Same approach can also be conducted to the surfaces, where nanoparticle embedded glass surfaces can be used (Figure 1b) as a biosensor platform (Himmelhaus & Takei, 2000). This strategy is more suited for Lab on a Chip applications since it provides the opportunity to produce multi-compartmental sensors with the ability to screen multivariate analysis with minimized sample volume (Kim et al., 2011). The limiting factors of working with such system are, first, obtaining the uniform metal nanoparticle deposited surface, and later surface biofunctionalization with the capture molecule and blocking agents, since most of the absorbance shifts may occur in these very first steps depending on the size of the capture molecule, a it effects the measurement sensitivity and narrows the linear range of sample concentration.

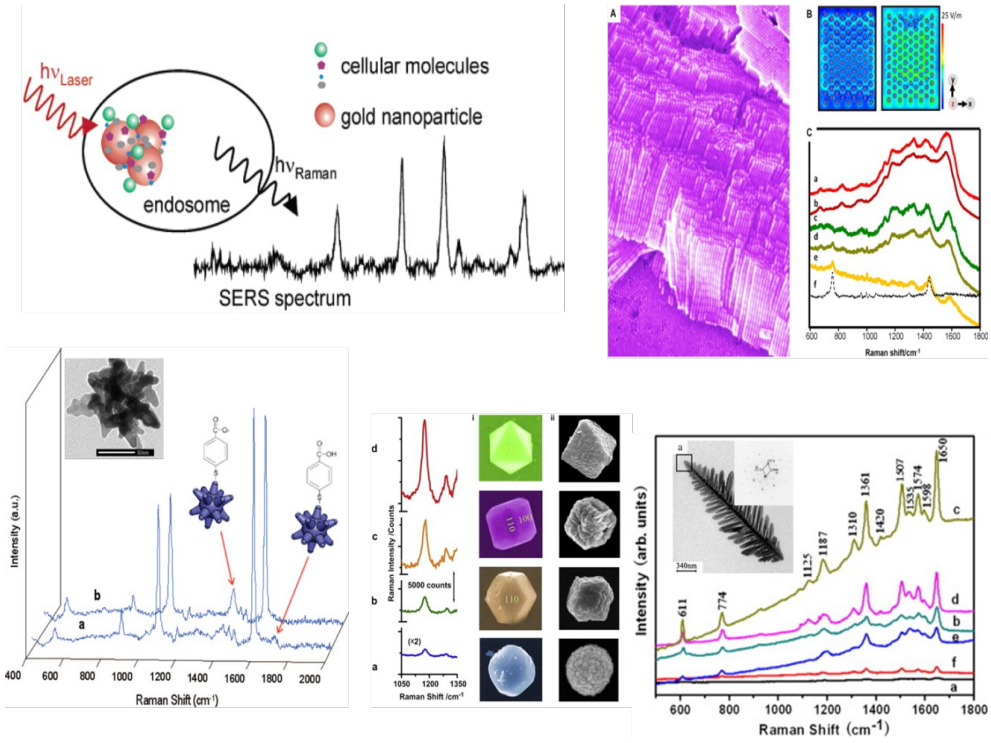

Figure 2. Introduction of different shaped gold and silver nanostructures to LSPR biosensors. Image reformatted from Alvarez-Puebla, Zubarev, Kotov and Liz-Marzán, 2012; Fang, Liu and Li, 2011; Khoury and Vo-dinh, 2008; Kneipp, Kneipp, McLaughlin, Brown and Kneipp, 2006; Yi, Chen, Chen, Luo, Wu, Yi et al., 2012.

Another technology that uses the localized SPR of nanoparticles for sensing is the surface enhanced raman scattering (SERS) (Tripp, Dluhy & Zhao, 2008) which is a powerful analytical tool provides quantification of trace constituents in biological and environmental samples, in many cases, with single-molecule sensitivity (Gunawidjaja, Kharlampieva, Choi & Tsukruk, 2009). Use of suitable nano-patterned surfaces or functionalized surfaces made up of metal nanoparticles can improve the raman signal up to 10^{15} fold (Pustovit & Shahbazyan, 2006). By this mean, both gold and silver are considered as noble materials for nanoparticle based SERS, however, they have drawbacks, too. For example, while silver shows larger SERS enhancements at visible and near IR region, gold possesses several advantageous properties over silver, such as higher performance, inertness, facile preparation and surface modification (Pustovit & Shahbazyan, 2006).

SERS platforms can be built from either deposited nanoparticles or graphed using nanolithography. Nanoparticles with tunable gaps by use of various linkers and bridge molecules alters the SERS signal more effectively while sensor surfaces constructed with these strategies still shows lack of reproducibility. Thus, there are several attempts for constructing sensor platforms with enhanced signal, reproducibility, sensitivity and stability via conducting different shaped nanostructures, as depicted in Figure 2 (nanocages, nanorod, nanowires, nanostars and dentric nanostructures) (Alvarez-Puebla et al., 2012; Fang et al., 2011; Kattumenu, Lee, Tian, McConney & Singamaneni, 2011; Khoury & Vo-Dinh, 2008; Ranjan & Facsko, 2012; Schütz, Steinigeweg, Salehi, Kömpe & Schlücker, 2011; Yi et al., 2012), as well as, developing new generation composites and hybrids with other structures including carbon nanotubes (Beqa, Singh, Fan, Senapati & Ray, 2011; Jiang et al., 2011), silica (Guerrini & Graham, 2012; Gunawidjaja et al., 2009) and quantum dots (Rumyantseva, Kostcheev, Adam, Gaponenko, Vaschenko, Kulakovich et al., 2013).

Besides the optical properties of the gold and silver nanoparticles, they are also appreciated members of electrochemical sensors. As defined by IUPAC, electrochemical sensors are "Self-contained integrated devices, which are capable of providing specific quantitative or semi-quantitative information using a biological recognition element (biochemical receptor) which is retained in direct spatial contact with an electrochemical transduction element." (Thévenot, Toth, Durst & Wilson, 1999) and are still lead the way for biomolecule detection among the other analytical approaches.

One of the known problems of electrochemical sensing of proteins is to find the suitable mediator for building the right connection between the active side of the protein and the electrode. Deposited gold nanoparticles on sensor surfaces were reported as they act like mediator which comforts the protein's free orientation and leads direct electron transfer through quantum tunneling effect. (Guo & Wang, 2007). Not only their conductivity but also catalytically properties due to high surface area, and electron density are abundantly employed to sensor technology. When colloidal gold at acidic conditions oxidized electrochemically, it produces reduced $AuCl_4^-$ ions, and in this way analyte can be quantified by measuring the change in the reduction current (Omidfar, Khorsand & Azizi, 2013). Reports consist of several other novel strategies using various types of gold nanostructures for the detection of molecules such as glycoproteins, growth factors, viruses and even metabolites directly from the cells, are exist in the literature and reader is directed to very valuable recent reviews and articles on the progress so far. (Ankri, Peretz, Motiei, Popovtzer & Fixler, 2012; Cheng, Huan & Yu, 2012; De La Escosura-Muñiz & Merkoçi, 2011; Liu, Wang & Lin, 2006). In some of these strategies, systems combining gold nanoparticles with other functional nanomaterials (carbon nanotubes, denritic nanoparticles, silica nanoparticles and magnetic nanoparticles, so on) were reported in order to

increase the sensitivity and analyte-ligand interaction, as well as maintaining the physiological environment. A very interesting example is the study of Costa et al. in which they used gold nanoparticles as label and redox-element in magnetoimmunoassays for Humana IgG detection (Costa et al., 2010). While magnetic nanoparticles used to pre-concentrate the analyte and deposit them on sensor surface, gold nanoparticle label provided catalytic system revealing Hydrogen Evolution Reaction (HER) in acidic conditions (Figure 3).

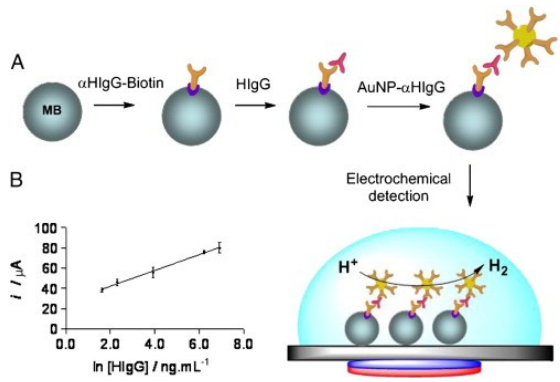

Figure 3. Gold nanoparticles (AuNPs) catalyzed Hydrogen Evolution Reaction (HER) at acidic environment which is for electrochemical detection of human IgG (Costa et al., 2010).

Silver nanoparticles and other nanostructures including nanowires and dendritic forms on the other hand, displays advantageous features same as gold, including easy dissolution, oxidization without additional chemicals and better electrochemical properties providing signal amplification (Yang, Hua, Chen & Tsai, 2013; Yi et al., 2012). For both gold and silver based nanostructures, homogenous deposition of them to the electrode surface and effectiveness of the functionalization are critical points to sustain sensor selectivity and the performance.

2.2. Quantum Dots

Fluorescent labels, mostly organic dyes such as rhodamine derivatives, fluorescein and cyanine dyes, are indisputable members of biosensors and bioassays. However, due to limitations of traditional fluorophores, for example; short band range, low stability by means of photo-bleaching and photo-oxidation, and short fluorescence lifetime, attentions are directed to a new generation inorganic, semi-conductive florescent nanoparticle, so called quantum dots (QDots) (Resch-Genger, Grabolle, Cavaliere-Jaricot, Nitschke & Nann, 2008). These nanoparticles show unique fluorescence properties which overcomes aforementioned limitations of organic fluorophores. Compared to the traditional dyes, inorganic QDots have higher resistance to the photobleaching, less sensitive to their local environment with narrower and symmetric fluorescence spectra which offer longer times of measurement (Bang & Kamat, 2009; Michalet et al., 2005; Resch-Genger et al., 2008). Most importantly, various types of quantum dots which emit light with exceptionally pure and bright colors with changing bulk band gap energies can easily be obtained by simply tuning their size or the formulation (Figure 4) (Asokan, Krueger, Alkhawaldeh, Carreon, Mu, Colvin et al., 2005). Quantum dots synthesized from several semiconductor materials in which they can be classified as II-VI type QDots from CdS, CdSe,

CdTeI; III-V type QDots from InP, InAsI and IV-VI type QDots from: PbSeI (Michalet et al., 2005). Besides, with their core-shell analogues, they are widely used as label in bioimaging, diagnosis, and drug delivery/tracking (Asokan et al., 2005; Dabbousi, Rodriguez-Viejo, Mikulec, Heine, Mattoussi, Ober et al., 1997). Combining QDots as label for different targets offers quite versatile tool for designing multiplex detection systems (Koehne, Chen, Cassell, Ye, Han, Meyyappan et al., 2004; Lowe, Dick, Cohen & Stevens, 2011; Rissin, Kan, Song, Rivnak, Fishburn, Shao et al., 2013). Introduction of nanomaterials to barcode amplification detection methods enables multivariant detection of proteins at submicron concentrations (Hill & Mirkin, 2006; Nam, Wise & Groves, 2005; Zhang, Carr & Alocilja, 2009). QDots with wide range of colors are versatile tools for barcoding. For example, a barcode assay system combining advantages of QDots and magnetic beads together in a single microfluidic system was reported by Gao et al, where they successfully demonstrated the multiplex recognition of four genetic targets; HIV, hepatitis B (HBV) and syphilis (Treponema pallidum) with a detection limit reaching to nM (Gao, Lam & Chan, 2013).

Another important strategy where QDots are effectively used is Förster resonance energy transfer (FRET) based sensing systems. The FRET phenomenon emerges as a result of a distance-dependent interaction which chromophore (a donor and an acceptor molecule) at close proximity (Wegner, Lanh, Jennings, Jain, Fairclough et al., 2013). In these systems, there is a signal ON-OFF switch which regulated by changes in the close proximity (maximum 10 nm) between FRET pairs as a result of target-host interaction (Lowe et al., 2011). In this scenario, while the quantum dots are mostly act as donor; acceptor can be either QDots, fluorescent dyes, proteins or metal and metal nanoparticles. A multiplex analysis time gated FRET based detection system for measuring protease activity was reported by use of single QDot as both donor and acceptor in contrary to the traditional multiplex analysis devices with multiple QDot label (Algar, Malanoski, Susumu, Stewart, Hildebrandt & Medintz, 2012). Qdot were coated with peptidic substrates designed for trypsin and chymotrypsin which labeled with florescent Terbium, Tb, (donor) and another fluorophore A_{647} (acceptor). As a result, real time protease activity was measured through the cleavage of peptide substrates resulting in photoluminescence intensity change in Tb, QDot, and A647 giving two distinct analytical signals (Figure 4a). The designed approach offers a versatile real time detection strategy with full-package of information on the protease activity including substrate/product concentrations, initial reaction rates, enzyme-substrate specificity constants (Kc/Km), and apparent inhibition constants with no significant cross contamination (Ki). This type of FRET based strategies can be extended to several other examples (Merkoçi, 2009).

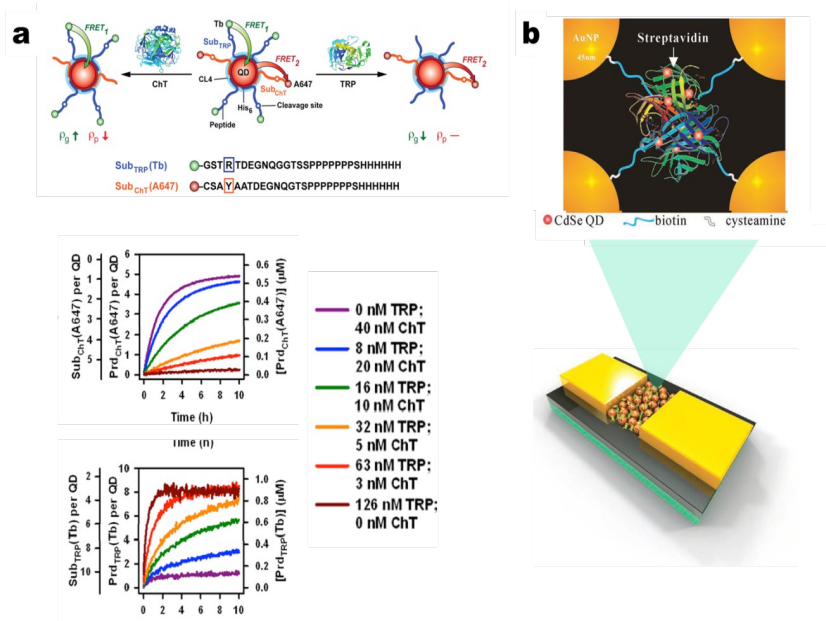

Figure 4. a) (Upper) Schematic of a time-gated FRET for multiplexed protease sensing using single QDot and its surface functionalisation with two labeles with either Tb or A647, serve as substrates for different proteases, where the cleavage sites are highlighted in the peptide sequences. (Buttom) Fluorescence signal at mixtures of different concentrations of TRP (8−126 nM) and ChT (3−40 nM) (Algar et al., 2012) b) reformed image of CdSe Quantum Dots enhanced nanogap devices for analysis of streptavidine-biotin pair as model target system (Yu, Chen, Wei, Liu, Yu & Huang, 2012).

Last but not the least, as explained in Section 2.1, in quantum gap regulated biosensor studies, the nanogaps in between metal nanoparticles are used as conducting bridges allowing direct flow of electrons (Li, Hu & Zhu, 2010; Lin, Bai & Huang, 2009). Once the analyte paired with its substrate/ligand in the nanogap (Figure 4b), it quickly reforms a strong electrical signal, which is applicable to the detection of any target from atoms to macromolecules (Li et al., 2010). Regarding to in situ growth of nanoparticles on the electrode surface, the aim is obtaining nanoparticles localized in close proximity enough for the electron tunneling. However, the dilemma of this methodology is that, to obtain nanogaps close enough (<5 nm), high number of nanoparticle is required and this naturally drives nanoparticles to agglomeration which reveals heterogeneous film on the electrode (Zhu, Zhang, Guo, Wang, Liu & Zhang, 2012). Whereas, introducing quantum dots to the nanogap based systems would overcome this drawback by propagating a supporting bridge conducting the nanoparticles grown at considerably lower concentrations, and thus, localized with larger gap interval (Yu et al., 2012). By this way, QDots could not only build a connecting bridge between nanoparticles and enrolled in signal enhancement, but also, they can regulate the electron tunneling path first between nanoelectrodes (AuNPs) and in big picture between the microelectrodes (Dahnovsky, Krevchik, Semenov, Yamamoto, Zhukovsky, Aringazin et al., 2005).

Despite many advantages of QDots as fluorescent label and signal transducer and/or enhancer in biosensing/bioimaging approaches, there are some negative aspects to be clarified before

widening their use in clinical applications. They might be cytotoxic leading cell apoptosis, they are not biodegradable, and accumulation of them in certain tissues and organs might result in further problems (Amna, Van Ba, Vaseem, Hassan, Khil, Hahn et al., 2013; Knight & Serrano, 2006; Winnik & Maysinger, 2013). Moreover, their optical properties can randomly vary over time. A phenomenon regarding to these variations is quantum-dot "blinking" which is associated with mobile charges on the nanoparticle surface (Frantsuzov & Marcus, 2005; Lee & Osborne, 2009). However, indispensable Pros of quantum dots over organic dyes shadow any of these negative aspects and carry them among the top nanomaterials list for future developments in biosensor development.

2.3. Magnetic Nanoparticles

Magnetic nanoparticles (MNP) which show size depended superparamagnetism have possessed great success in separation processes. These nanoparticles with no magnetic memory -they exhibit their magnetic behavior only when an external magnetic field is applied- have the advantage over bulk counterparts with no agglomeration after a proper surface modification or coating (Mody et al., 2010). Polymers, lipids, silica and amphipathic molecules have been successfully used as coating material for not only prevent from precipitation but also favor the further functionalization of them with active molecules (Alwi, Telenkov, Mandelis, Leshuk, Gu, Oladepo et al., 2012; Floris, Ardu, Musinu, Piccaluga, Fadda, Sinico et al., 2011; Goldhawk et al., 2012; Kim, Mikhaylova, Wang, Kehr, Bjelke, Zhang et al., 2003; Mikhaylova, Kim, Bobrysheva, Osmolowsky, Semenov, Tsakalakos et al., 2004; Sawant, Sawant, Gultepe, Nagesha, Papahadjopoulos-Sternberg, Sridhar et al., 2009). Among all types of magnetic nanoparticles, iron oxides (magnetite and maghemites) are found to be more potent for analytical uses due to their being inert and also their FDA certified biocompatibility, and low level of toxicity (Gupta & Gupta, 2005; Yu, Jeong, Park, Park, Kim, Min et al., 2008). Although, most of the studies on the use of magnetic nanoparticles in biosensor development, they were used as separating tools in order to eliminate washing steps or attaching the sensing bodies on to the biosensor platform via magnetic field, there are increasing number of studies on the use of physicochemical properties of MNPs for sensing (Chemla, Grossman, Poon, McDermott, Stevens, Alper et al., 2000; Mody et al., 2010; Peng, Liang, Zhang & Qiu, 2013; Zhang, Carr et al., 2009).

Published study from Trahms's Lab in 1997 on a of superconducting quantum interference device (SQUID)-based detection system for the interaction of biomolecules is one of the first examples in which magnetic nanoparticles used as sensing body (Kötitz, Bunte, Weitschies & Trahms, 1997). This label free immunosensor bases mainly on the difference in magnetic relaxation time of magnetic nanoparticles before and after the reunion of target molecule (antigen) and the recognition element (antiobody) which is immobilized onto particle surface (Chemla et al., 2000; Titz, Matz, Drung, Hartwig, Groû & Ko, 1999).

In a more recent study, Baratella, Magro, Sinigaglia, Zboril, Salviulo and Vianello (2013) used maghemite nanoparticles attached on a carbon paste (CP) electrode as hydrogen peroxide electro-catalyst, and reported an oxidase based reagentless glucosensor device with a sensitivity of 45.85 nA $\mu M^{-1}cm^{-2}$, and a detection limit of 0.9 µM (Baratella et al., 2013). Same approach was conducted by incorporating magnetic nanoparticles to an exfoliated graphene oxide sheet with carboxyl-long-chains together with glucose oxide and poly[aniline-co-N-(1-one-butyric acid) aniline] (SPAnH) (Yang, Tjiu, Fan & Liu, 2013). In this study, glucose (they also detected hydrogen peroxide) was detected with sensitivity higher than that reported by Bratella et al. (1074.6 $\mu A\ mM^{-1}\ cm^{-2}$), however with a poorer linear detection range in mM level.

Esseghaier and Zourob were used magnetic particles with a handy procedure in order to detect HIV-1 protease which is essential for the HIV for the maintenance of its reproduciblity (Esseghaier & Zourob, 2012). They first built SEMs of peptide (HIV-1 protease substrate) conjugated magnetic particles constructed on gold electrode. Cleavage of the protease substrate by addition of HIV-1 protease under appropriate magnetic field, results in dissociation of the MNPs from the sensor surface (Figure 5). That kind of dissociation leads an electrochemical and optical signal change which is expected to be proportional to the target concentration. Authors claimed a detection limit as low as 100 pg HIV-1 protease /mL. This strategy could have potential with applicability to several other enzymes capable of cleaving, and can be extended to other types of biomolecules by designing engineered bridge molecules.

One other detection approach that we come across often is Giant-magnetoresistive (GMR) type sensors where the signal is measured due to the change in the resistivity of a material or a structure as a function of an external magnetic field. Due to claimed high sensitivity and quick response, GMR sensors have been utilized in many areas of science and technology including biosensor development with increased demand on materials showing high magnetoresistance. One of the examples of GMR sensors is the investigation of the uptake of macromolecules by cells. In such examples, magnetic beads left to reach with the cells, which previously grown on the biochip surface by sedimentation, and the progress of particle uptake, so that of phagocytosis, was monitored real-time by measuring the change in signal on a biochip system (Shoshi, Schotter, Schroeder, Milnera, Ertl, Charwat et al., 2012). In another example, Kim and Wang reported a magneto-nanosensor biochip for fungal detection by use of giant magnetoresistive (GMR) spin-valve sensor array in which biomarkers were successfully detected at pictogram levels (Dokyoon & Wang, 2012). These examples can be extended to genotyping of human hepatitis B virus (HBV), DNA and many other biomarkers (Li, Jing, Yao, Srinivasan, Xu, Xing et al., 2009; Xu, Yu, Han, Osterfeld, White, Pourmand & Wang, 2008). In addition to aforementioned analytical approaches, there are many other strategies aiming to make full potential of these unique materials (eg. fluxgate sensor (Baltag & Costandache, 1997; Ripka, 2003), Hall effect sensor (Volmer & Avram, 2013) and induction coil (Tumanski, 2007), exc.) in analytical chemistry. However, there are still more steps to be taken for understanding the magnetic behavior of them and finding better approaches for surface biofunctionalisation avoiding aggregations and loss of magnetic properties.

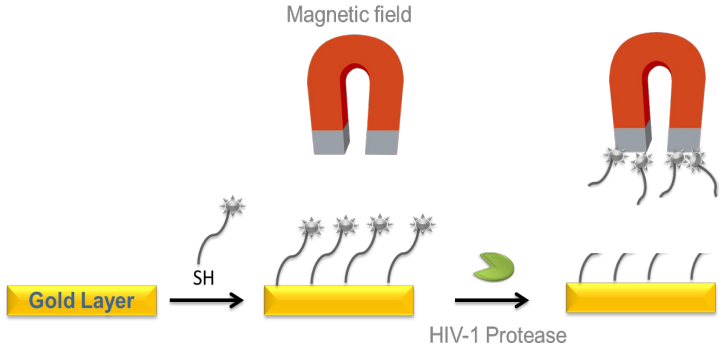

Figure 5. Mechanism of HIV-1 protease detection by magnetic nanoparticles. Reprinted from Esseghaier and Zourob, 2012.

2.4. Carbon nanotubes

Carbon nanotubes (CNT) are carbon based tubular structures formed from two dimensional graphene sheets with nanometer-size diameters and micrometer lengths (Jorio, Dresselhaus, Dresselhaus, 2008). They hold excellent mechanical stiffness and chemical stability. Although, their history goes back to early 50s, CNTs became popular and noticed by scientific community after the paper published by Sumio Iijima in 1991 (Iijima, 1991). There are several techniques for the synthesis of carbon nanotubes with well-defined structure and dimensions (Dresselhaus, Dresselhaus & Avouris, 2001; Ren, 2007; Shanov, Yun & Schulz, 2006) as well as wall number (single wall, multi wall ext.) but demands on greener and facile synthesis methodologies are uprising. Since the first report focused on the catalytically properties of CNTs and their possible potential as biosensor element published in 1996 to present day, over 2000 articles and reviews were published according to Science Direct records in which over thousands of them were published in the last 5 years. This increased urge to the subject is due to their extraordinary mechanical features and conductivity in addition to their highly reactive surface with possibility to be functionalized with any molecule, making them ideal tools for the development of nanoelectronic devices, circuits and sensors (Balasubramanian & Burghard, 2006; Dresselhaus et al., 2001; Putzbach & Ronkainen, 2013). The surface functionalization of the CNTs with bacteria, aptamer, DNA, polymers, enzymes, metal nanoparticles and cells were demonstrated and used as multifunctional sensor platforms in Lab-on-Chip technologies (Bareket-Keren & Hanein, 2012; Chiariello, Miano & Maffucci, 2009; Choong, Milne & Teo, 2008; Yantzi & Yeow, 2005). Rius group published an aptosensor where they used high-affinity RNA aptamer that specifically binds to type IVB pili of Salmonella Typhi as recognition element (Zelada-Guillén, Riu, Düzgün & Rius, 2009). They immobilized aptamer onto the carbon nanotube, which horizontally attached to glassy carbon electrode through Π-Π stacking (Figure 6c). By detecting the charge changes due to a conformation change of aptamer as a result of its interaction with bacteria, they reported the possibility to detect extremely low concentrations of bacteria without cross reaction with other types of bacteria. A close strategy using glycosylated single walled CNTs (Figure 6c) was used to direct detection of secreted metabolites and biomolecules from cells (Sudibya, Ma, Dong, Ng, Li, Liu et al., 2009). These noninvasive methodologies for cell based detection can be extended to several other examples, such as genetic material, propteins, enzymes, aminoacids, cell proliferation, cancer biomarkers and viruses (Boero, Olivo,Carrara & De Micheli, 2012; Han, Doepke, Cho, Likodimos, de la Cruz, Back et al., 2013; Koehne et al., 2004; Lata, Batra, Kumar & Pundir, 2013; Merkoçi, 2009; Pandiaraj, Madasamy, Gollavilli, Balamurugan, Kotamraju, Rao et al., 2013; Yang et al., 2013; Zhang, Guo et al., 2009).

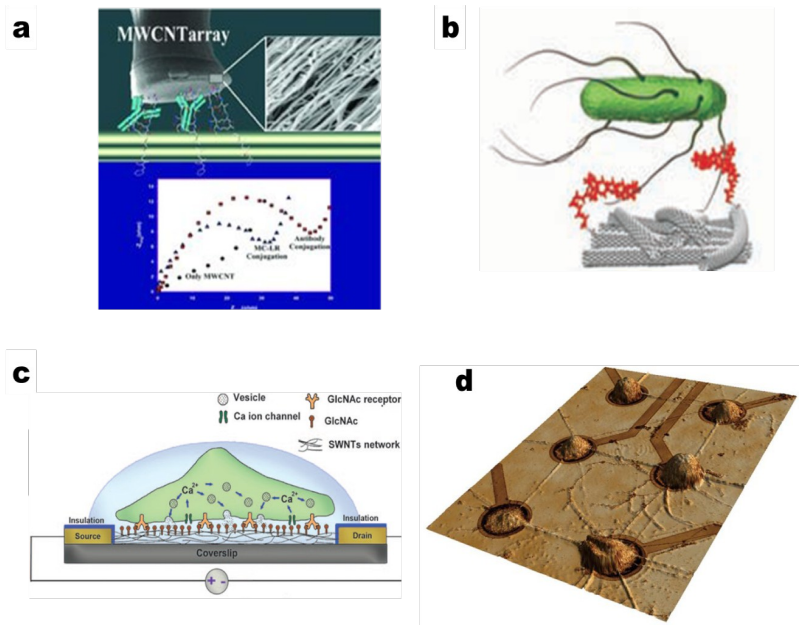

Figure 6. An assortment of different approaches for employing carbon nanotube as a part of biosensor for detection of various targets: a) Multiwalled-Carbon-Nanotube-Based biosensor for monitoring microcystin-LR in drinking water supplies (Han et al., 2013), b) aptamer based detection of bacteria on carbon nanotube embedded electrode (Zelada-Guillén et al., 2009), c) real time analysis of dynamic secretion from cells (Sudibya et al., 2009), and d) Neuro-gliacortical cell culture from embryonic rats grown on a carbon nanotube microelectrode array (Bareket-Keren & Hanein, 2012).

There are other approaches in which the shape of the CNTs comes forward. The 2D and 3D assembly of these high aspect ratio structures hollow inside, results in enormous high surface areas tasking account both the exterior and interior which allows not only immobilization of bioactive molecules on each CNTs but also forming highly catalytic surface allowing direct electron flow (Gomez-Gualdron, Burgos & Balbuena, 2011; Yang, Thordarson, Gooding, Ringer & Braet, 2010). AMES Research Center, NASA, researchers reported a label free DNA microchip built up of vertically aligned multiwalled carbon nanotubes (MWCNTs) by wafer-scale plasma enhanced chemical vapor deposition (PECVD) method (Koehne et al., 2004). The probe molecules (antibody, nucleic acids vs.) were attached to the tips of MWCNTs and analyte concentration was directly measured from oxidized guanine signal with several fold higher sensitivity, low detection limit and with multiplex property.

High aspect ratio CNTs also found a lot of use in the formation of composites where they have been employed for the growth of various kinds of metal and metal oxide coated or decorated nanotube structures and composites (Ajayan, Stephan, Redlich & Colliex, 1995; Chastel, Flahaut, Peigney & Rousset, 2000; Chen, Hu, Shao, Li & Wang, 2009; Harris, 2004). These catalytically or optically activated sensor surfaces demonstrated high sensitivity and selectivity for the label free detection of biomolecules. (Baro, Nayak, Baby & Ramaprabhu, 2013; Jiang et al., 2011; Kumar, Mehdipour & Ostrikov, 2013)

Despite their huge potentials in sensor technology, the non-ideal (or even cytotoxic) interface between CNTs and the living cells, asbestos like pathogenicity, limits their application to biological systems and wider use (Ali-Boucetta, Nunes, Sainz, Herrero, Tian, Prato et al., 2013; Osmond-McLeod, Poland, Murphy, Waddington, Morris, Hawkins et al., 2011; Poland, Duffin, Kinloch, Maynard, Wallace, Seaton et al., 2008), thus, new coating materials and strategies in order to overcome biocompatibility issues as well as new synthesis techniques to increase deposition homogeneity and to make the *in situ* nanotube growth easier are strongly required.

3. Conclusions and Future Aspects

Today scientists are capable of developing sensing systems to detect biomarkers, essential proteins, genetic material, and so on, with the help of nanotechnology. Nanotechnology holds a great potential for imaging, diagnosis and therapy, where different nanostructures from different material could be used as labels, signal enhancers, catalyst and as tools to build sensor platforms. The final aim is to obtain efficient techniques for improved real-time molecular imaging, monitoring drug trafficking, as well as development of Lab-on-a-Chip devices capable of detecting diseases and report real-time. Although, still the use of them in clinical requires extensive effort, there are several ongoing projects worldwide aiming to understand the basis of nanoworld. The forthcoming years would see their potential applications in building Lab-on-Chip system for home-based point-of-care diagnosis. However, how much harmful are those nanoparticles and nanostructures to the living organisms and environment is still a major question to be concerned and should be resolved before they engaged to in bio-related areas.

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