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Array-based sensing with nanoparticles: "Chemical noses" for sensing biomolecules and cell surfaces

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Abstract

Nanoparticle-based arrays have been used to distinguish a wide range of biomolecular targets through pattern recognition. In this report, we highlight new "chemical nose" methodologies that use nanoparticle systems to provide high sensitivity sensing of biomolecular targets, including fluorescent polymer/gold nanoparticle complexes that can discriminate between different bioanalytes including proteins, bacteria, and mammalian cells as well as dye-based micellar systems for the detection of clinically important metallo- and non-metallo proteins.

1. Introduction

Most biological recognition processes occur via specific interactions. However, sensory processes such as taste and smell use "differential" binding where the receptors bind to their analytes through interactions that are selective rather then specific [1,2]. These array based sensing platforms can be trained to generate a response pattern analogous to olfaction, providing versatile detectors [3]. Recently, a variety of array based sensor platforms have been developed for biomacromolecule sensing, including porphyrins [4], oligopeptide functionalized resins [5], and polymers [6,7].

Nanoparticles (NPs) feature sizes commensurate with biomacromolecules, coupled with useful physical and optical properties [8,9]. Modulation of these physicochemical properties can be readily achieved by changing of core and/or ligand structure. In this report, we highlight the recent advances of array based/chemical nose sensors using materials such as gold, dendrimer, and magnetic nanoparticles for the detection and identification of analytes such as proteins, bacteria, and cells.

2. Nanoparticle arrays for sensing proteins

Irregular protein concentration levels in biofluids, e.g., serum, urine, and saliva, provide essential information for the early diagnosis of many pathological conditions [1,10,11,12,13,14]. Substantial efforts have been devoted to developing precise and efficient methods for protein sensing [15] including enzyme-labeled immunoassays [16], electrophoresis methods [17], and analytical techniques [18]. Detection and identification of imbalance through of an array-based sensing approach provides a promising alternative to these methods [5]. Array-based sensing approaches are complementary to more traditional

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immunosensing strategies (e.g. ELISA), providing versatile systems that can be "trained" to recognize analytes and potentially disease states. In 2007, Rotello *et al.* fabricated a sensor array composed of six cationic functionalized gold nanoparticles (AuNPs) and an anionic PPE polymer that can properly identify seven common proteins [19••]. The polymer fluorescence is quenched by gold nanoparticles; the presence of proteins disrupts the nanoparticle–polymer interaction (Figure 1a), producing distinct fluorescence response patterns (Figure 1b) based on particle-protein affinity. The effeciency of this system is attributed to both the quenching ability of AuNPs as well as the 'molecular wire' effect of PPE polymer [20]. Since the protein-nanoparticle interactions are determined by their respective structural features such as charged, hydrophobic, hydrophilic, and hydrogen-bonding sites [21], the differing affinities lead to a fluorescence response fingerprint pattern for individual proteins (Figure 1b). The raw data responses obtained were subjected to linear discriminant analysis (LDA) [22,23] to differentiate the fluorescence patterns of the nanoparticle–PPE systems against the different protein targets. This system showed a limit of detection of 4–215 nM depending on M_w protein and identifed correctly 52 out of 55 unknowns samples (94.5% accuracy) [19••].

Polymeric nanoparticles provide a separate class of scaffolds for sensor design. Thayumanavan *et al.* developed a polymeric micellar nanosystem that responded to electronic complementarity, allowing the system to be selective for metalloproteins [24]. They used eight different fluorescence dye molecules non-covalently bound to the micellar interior of an amphiphilic homopolymer to generate a pattern that allowed the differentiation of four different metalloproteins with limits of detection of 1–200 μM. In another approach, Thayumanavan *et al.* reported a micellar disassembly process for transduction [25]. Five different noncovalently assembled receptors were generated, and the disassembly was studied by monitoring the encapsulated dye release in response to five different non-metalloproteins. The disassembly-induced fluorescence change of the guest molecule produces protein-specific patterns. The limit of detection in this approach was 8 μM. More recently, Thayumanavan *et al.* introduced a new method where the differential response was generated from a single polymer-surfactant complex with two approaches, i.e. the disassembly and guest release based pathways and photoinduced charge/energy transfer quenching (excited state quenching) (Figure 2a). By varying the transducer using non-metalloprotein and metalloproteins [26•] they were able to generate a limit of detection for non-metalloproteins of 8 μM (Figure 2b). In the case of the metalloproteins, the limit of detection was 80 nM (Figure 2c). Thayumanavan *et. al* also studied the use of a fluorescent anthracene-core dendrimer system that has carboxylic acid groups on the periphery that affords a differential response protein pattern though the binding energy transfer process at analyte concentrations between 1–5 μM [27]. Upon binding, an energy transfer process occurs with quenching of the fluorescent core. The interchange between quenching and binding lead to differential responses that allowed discrimination of 3 different metalloproteins.

The above studies focused on protein sensing in buffer. The plasma/serum proteome, in contrast, contains more than 20,000 different proteins and an overall protein concentration of ~1 mM, (71 mg ml^{-1}), providing a complex matrix for sensor design [28,29]. To construct a more effective protein sensing system, Rotello *et al.* selected green fluorescent protein (GFP) [30], a stable dimeric biomolecule used as transducer. The use of GFP minimizes aggregation, improving sensor efficiency as compared with the previous method using conjugated polymers. In this sensing process, the biocompatible AuNP/GFP conjugated array was able to identify five of the more abundant human serum proteins, i.e. human serum albumin, immunoglobulin G, transferrin, fibrinogen and α–antitrypsin, (Figure 3a) in an undiluted solution of human serum (overall protein concentration *~1 mM*), obtaining a limit of detection of 500 nM [31•]. Further experiments indicated that mixtures

of different proteins and the addition of one protein in different concentrations also led to a specific and reproducible change in the LDA-based patterns (Figure 3b).

The sensitivity of fluorophore displacement strategies is limited by the inherent emissivity of the transducer. To overcome this limitation, Rotello *et al.* used enzyme-amplified array sensing (EAAS) to provide a platform with enhanced sensitivity [32••]. Functionalized cationic AuNPs electrostatically bind to the anionic *β*-Galactosidase (*β*-Gal), reversibly inhibiting the enzyme (Figure 4a) [33]. Displacement of the particle by analyte proteins restores *β*-Gal activity towards a fluorogenic substrate, generating a readout signal that is amplified through enzymatic catalysis. This EAAS system couples the signal amplification process of ELISA with the versatility of the "chemical nose" approach, as it is able to sense and identify a range of biomedically relevant proteins with a limit of detection of 1 nM in both buffer as well as in desalted urine solution (Figure 4b).

3. Nanoparticle arrays for sensing bacteria and mammalian cells

The efficient detection of pathogenic microorganisms is of great importance in clinical, forensic, medical, and environmental sciences [34]. In clinical diagnostics, bacterial infections are identified by plating and culturing, a time-consuming methodology. While several newer methods including PCR, have been used to detect specific microorganisms [35], a facile wet-chemical method for the timely detection and identification of microorganisms would be of interest in both a clinical setting as well to test for food spoilage in industrial settings [36].

Rotello *et al.* created an array-based sensing system based on non-covalent conjugates of AuNPs and a modified PPE that allows the detection of bacteria within minutes [37•]. As shown in Figure 5, the anionic PPE polymer is bound initially to the functionalized cationic gold nanoparticle creating a fluorescence-quenched species. When these complexes are exposed to bacteria in solution, there is a competitive equilibrium for the positively charged AuNPs by both the polymer species and the surface of the bacteria. Depending on the interaction of bacteria with the functionalized head group, there is a differential polymer release from the surface of the AuNP whose fluorescence is restored providing a readable response. To test the efficacy of this methodology, they were able to differentiate between 12 different bacteria that contain both Gram-positive (e.g. *A. azurea*, *B. subtilis*) and Gram-negative (e.g. *E. coli*, *P. putida*) species. As shown in Fig. 5c, LDA analysis of the fluorescence responses discerns not only the species, but also betweens strain of *E. coli* at 2×10^5 cells/mL. In initial studies, they were able to successfully identify 61 out of 64 unknowns (95% accuracy) taken from the training set, showing the inherent reliability of this system.

Recent research using nanoparticle arrays for cell surface identification has focused on the detection of cancer. Cancerous cells can be differentiated from non-cancerous ones on the basis of intracellular and extracellular (cell surface) biomarkers [38]. Cell detection based on cell surface protein biomarkers generally involves the development of specific antibodies [39,40,41]. Intracellular protein biomarkers [42] have been explored by emerging proteomic techniques, e.g. gel electrophoresis (2D-SDS-PAGE) [43] and mass spectrometry [44]. Although these lysate-based strategies provide a potential approach for cancer detection, they require both the presence and prior knowledge of intracellular biomarkers [45].

Rotello *et al.* have employed gold NP–fluorescent conjugated polymer constructs to differentiate normal cells from their cancerous and metastatic counterparts [46••]. Due to their cationic surfaces, the functionalized nanoparticles interact with cell surfaces through both electrostatic and hydrophobic/hydrophilic interactions. In their study, Three AuNP–PPE constructs were able to differentiate between cell types, but more significantly they are

able to differentiate between isogenic cell lines are either normal, cancerous, or metastatic, e.g. CDBgeo, TD, and V14 using 20,000 cells. To lower the detection limit of these systems, they were able to develop a differential patterning array biosensor using a complex of functionalized AuNPs with green fluorescent protein (GFP) [47] that effectively identified and differentiated between several types of normal, cancerous, and metastatic isogenic mammalian cancer cells. Changing only the transducer, they have been able to achieve high sensitivity and full differentiation of the mammalian cells at concentrations of ~5000 cells, a four-fold enhancement of sensitivity relative to prior NP-polymer sensors.

Using an alternate approach to transduction, Huang *et al.* reported a magnetic glyco-nanoparticle (MGNP) based nanosensor array system utilizing carbohydrates as the ligands to not only detect and differentiate cancer cells but also to quantitatively profile their carbohydrate binding abilities using magnetic resonance imaging (MRI) signatures (Figure 6) [48••]. These glyco-nanoparticles were incubated with the cell suspensions in media, and then analyzed by MRI for changes in transverse relaxation times (T2). Through this process, they were able to differentiate using LDA 10 different cell types at concentrations as low as 10^5 cells/mL (Figure 6c).

4. Conclusions

Based on the results presented in the review, it is apparent that nanoparticle-based sensors provide a powerful platform for analysis of proteins and cell surfaces. Through variation of sensor design it would appear that almost any system could be differentiated through appropriate sensor design. As we learn the strategies required for this differentiation, however, we will have to address the complexity of the target systems. Biofluids, such as undiluted human serum, contains a large amount of various proteins, salts, and cells that not only can inhibit or alter the sensing elements' ability to detect target analytes, but also complicate pattern generation. Clearly, creation of clinically useful sensor will require co-evolution of chemical and data analysis strategies.

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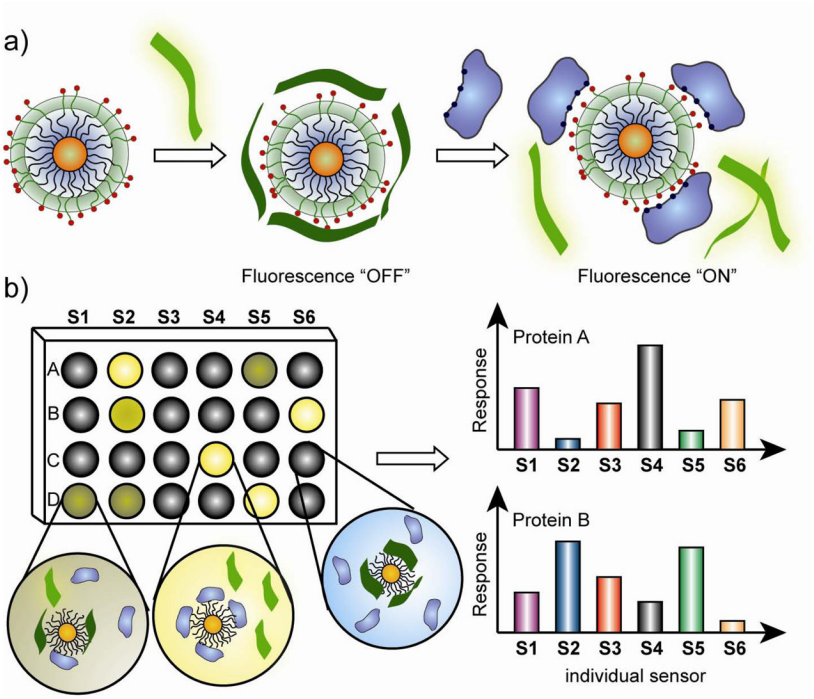

Figure 1.

Schematic illustration of 'chemical nose' sensor array based on AuNP-fluorescent polymer conjugates. a) The competitive binding between protein and quenched polymer-AuNP complexes leads to the fluorescence light-up. b) The combination of an array of sensors generates fingerprint response patterns for individual proteins [19].

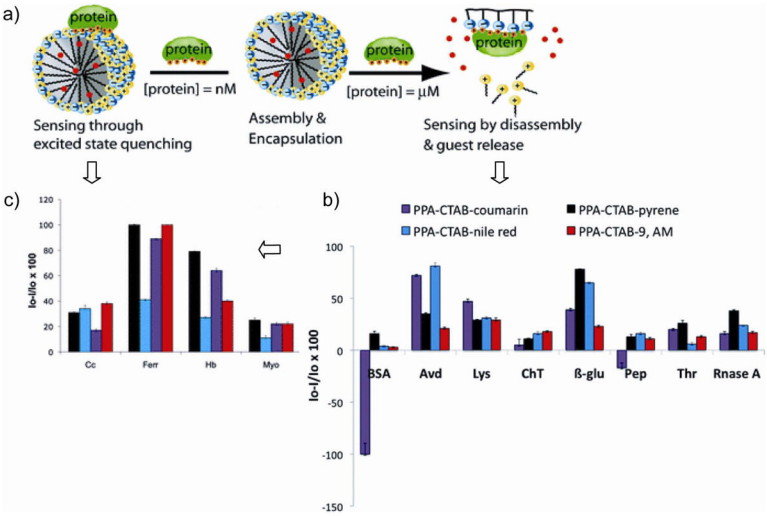

Figure 2.

a) Schematic of the fluorescence response due to metalloproteins/nonmetalloprotein either due to the disassembly or due to the energy/electron transfer based quenching for metalloproteins. b) Analyte-dependent patterns from emission changes at 8 μM concentration of the nonmetalloprotein. c) Analyte-specific sensing patterns for metalloproteins with different dye molecules at 80 nM concentration of proteins (coumarin (10^{-6} M; λ_{ex} = 400 nm); pyrene (10^{-6} M; λ_{ex} = 339 nm); nile red (10^{-6} M; λ_{ex} = 550 nm); 9-anthracene methanol (10^{-5} M; λ_{ex} = 365 nm)). Figure reproduced with permission from reference [26].

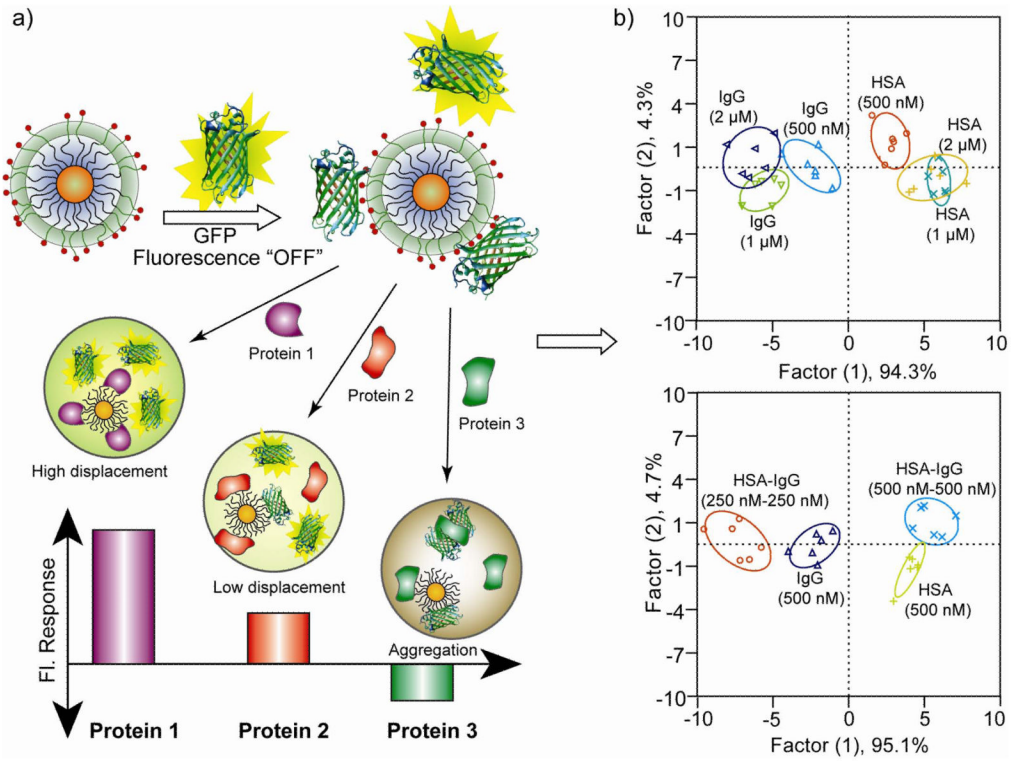

Figure 3. GFP-NP sensor array

a) Schematic illustration showing the competitive binding between proteins and quenched AuNP-GFP complexes whose aggregation leads to the fluorescence "turning on" or further quenching using a library of cationic nanoparticles. b) Discrimination of HAS and IgG at different concentrations and mixture of proteins. At the top, canonical score plot for the fluorescence patterns as obtained from LDA for HAS and IgG at different concentrations (500 nM, 1 μM, and 2 μM) with 95% confidence ellipses. At the bottom, HAS and IgG were mixed at 1:1 molar ratio with 250 nM each and 500 nM each, and added to five AuNP-GFP complexes. The canonical score plot obtained from LDA analysis were compared with those for the 500 nM individual proteins [31].

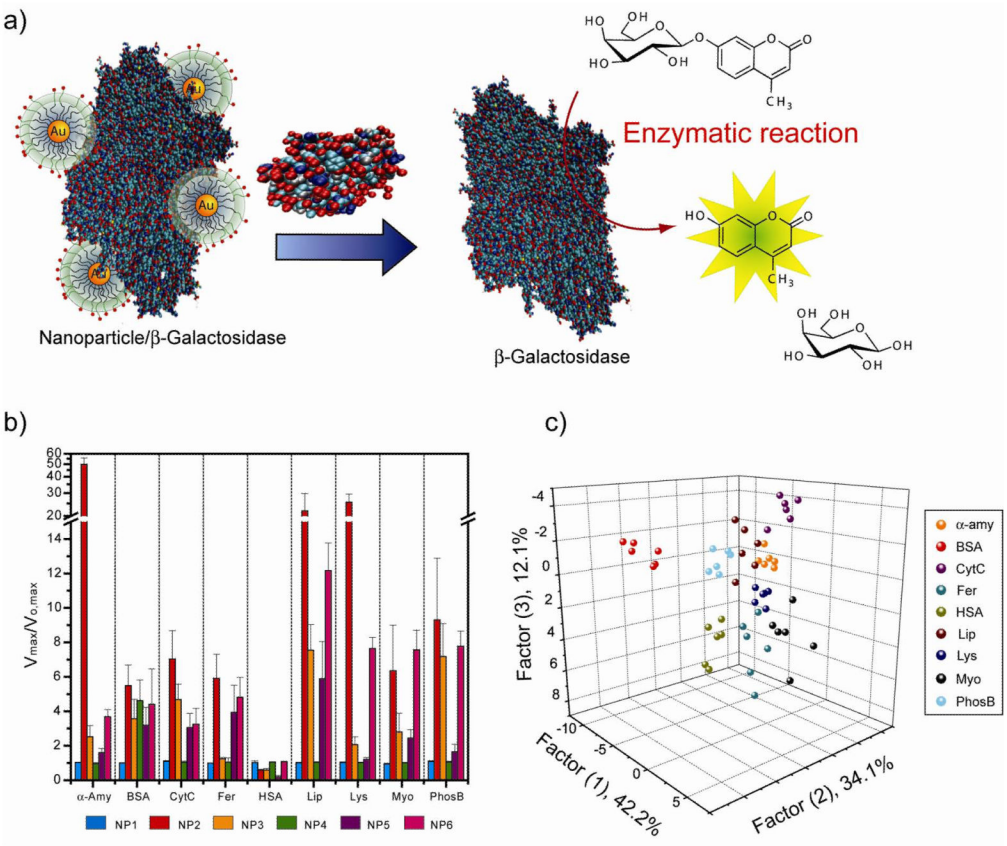

Figure 4.

A schematic representation of a sensor element in the sensor comprised of β-galactosidase (β-Gal) and cationic **AuNPs** and differentiation of proteins in 3-D. a) As shown, β-gal is displaced from the β-Gal/**AuNP** complex by protein analytes, restoring the catalytic activity of β-Gal towards the fluorogenic substrate 4-methylumbelliferyl-β-D-galactopyranoside, resulting in an amplified signal for detection. b) Differential protein pattern of the nine proteins at 1 nM. c) Canonical score plot of the first three factors of fluorescence response patterns obtained through β-Gal/**AuNP** sensor array against nine target proteins in 1 nM concentration [32].

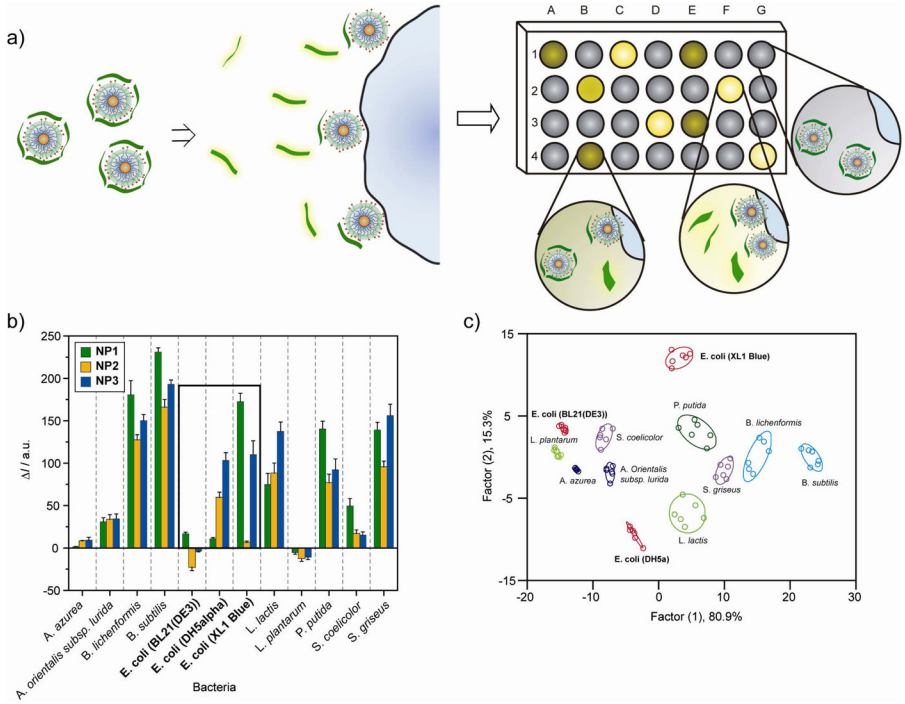

Figure 5.

Array-based sensing of bacteria. a) Schematic diagram of the displacement assay between bacteria and the NP-PPE complex. b) Fluorescence response (ΔI) patterns of the NP-PPE sensory array against various classes of bacteria (2×10^5 bacteria/mL). As shown on the plot, the same strains of bacteria can also be identified. c) Canonical score plot for the first two factors of simplified fluorescence response patterns obtained with NP-PPE assembly arrays against bacteria (95% confidence ellipses shown) [37].

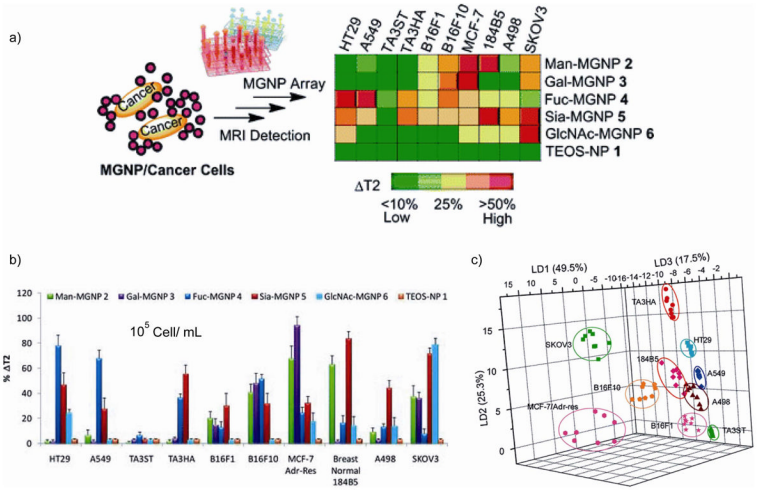

Figure 6.

a) Percentage changes of *T*2 relaxation time (%Δ*T*2) obtained upon incubating MGNPs **2**–**6** or the control NP **1** (20 μg/mL) with 10 cell lines (10^5 cells/mL). The Δ*T*2 was calculated by dividing the *T*2 differences between MGNP and MGNP/cancer cell by the corresponding highest Δ*T*2 from each MGNP category. b) LDA plots for the first three LDs of Δ*T*2 patterns obtained with the MGNP array upon binding with the 10 cell lines (10^5 cells/mL). Full differentiation of the 10 cell lines was achieved. Figure reproduced with permission from reference [48].