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Beyond Biomarkers: Identifying Cell State using Unbiased Nanosensor Arrays

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Summary

Traditional cell detection based on biomarkers relies on specific lock-and-key recognition. However, many diseases either do not have obvious biomarkers or these markers are currently unknown. Unbiased sensor arrays based on nanoparticles use selective interactions to generate bioprofiles capable of identifying cell type and state. As a result, these arrays can differentiate subtle variations on the cell surfaces, presenting a potential approach for personalized diagnostics.

Keywords

Unbiased sensors; Biomarkers; Cancer cells; and Nanoparticles

Rapid screening of cells and cell states is at the forefront of pharmaceutical and biomedical research. Traditional screening approaches rely on *specific* interactions that respond to predetermined biomarkers, i.e. specific indicators of a particular biological state or disease. For many diseases, however, obvious biomarkers have not been identified or are not present. Unbiased array-based methods provide an alternative strategy, allowing differentiation through selective recognition [1,2]. Independent of specific biomarkers, unbiased arrays are able to detect minute global changes on the cell. These *selective* arrays are able to discern subtle phenotypic alterations presented on cell surfaces. Unbiased arrays are composed of sensing elements that respond to non-specific interactions with analytes. Nanotechnology offers unique tools to create these unbiased sensors owing to the ability to precisely control the composition of sensor components, the multivalency of recognition elements, and the flexibility to control interactions at the nanoscale. These arrays provide a promising platform for bioprofiling and personalized screening for diseased states/progression.

The first unbiased sensor array developed for cell sensing was based on the electrostatic interactions between an anionic fluorescent probe and multiple cationic functionalized gold nanoparticles (AuNPs) [3,4]. Complexation with the nanoparticle quenches the probe fluorescence; upon incubation with cells in a 96 well plate, the probe is displaced from the surface of the AuNP due to competitive binding, regenerating the fluorescence (Figure 1). The observed response is modulated by both the particle surface functionality and the analyte. Combining the individual responses from wells each containing differently functionalized nanoparticles allows robust sample differentiation and classification after

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performing statistical classification. Isogenic healthy, cancerous, and metastatic mammalian cells were used as a test bed to access the efficacy of the method [5], with full differentiation obtained between all cell lines. Since the cells bear the same genetic background, differentiation stems from subtle phenotypic variations presented on the cell surfaces.

In more recent studies, other analytical detection techniques have been explored in the development of unbiased sensor arrays. For example, cancerous cells were detected in solution using a nanomaterial-assisted chemiluminescence array (Figure 2a) [6]. The thermochemiluminescence response of the array generated unique patterns upon addition of different cells to the sensor. Notably, they differentiated between normal and metastatic cell lines (Figure 2b). In another approach, iron oxide nanoparticles and nuclear magnetic resonance were used to differentiate cancer cells [7]. The detection and profiling of cells with this system is based on the differential interactions between the carbohydrate ligands of the nanoparticles (Figure 2c) and receptors presented on the cell surface. The commonality of these techniques is the reliance on selective interactions generating distinctive patterns recognized by the sensor.

While a relatively new tool, unbiased array-based sensors provide a potentially powerful tool for cell surface recognition. The discrimination of healthy, cancerous and metastatic cells exemplifies these sensors' potential for real world applications. The further development of these systems will rely on a fusion of nanomaterial design, chemometrics and bioinformatics to generate more complex and useful bioprofile patterns that could provide a new path to personalized diagnostics.

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Biographies

Bradley Duncan received his H.A.B. degree in Chemistry from Saint Anselm College in 2009. Currently, he is a Ph.D. student in the Department of Chemistry at the University of Massachusetts-Amherst under the guidance of Professor Vincent M. Rotello. His research focuses on the self-assembly of nanoparticles at the liquid–liquid interface and the fabrication of colloidal micro/nanocapsules for delivery applications.

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Vincent M. Rotello is the Goessmann Professor of Chemistry at the University of Massachusetts. He has received the NSF CAREER, Cottrell Scholar, Dreyfus Teacher-Scholar, Sloan Fellowship, and the Langmuir Lectureship, and is a Fellow of the American Association for the Advancement of Science and the Royal Society of Chemistry (U.K.). He is an Associate Editor for the *Journal of Materials Chemistry* and Executive Editor for *Advanced Drug Delivery Reviews*. His research focuses on using chemistry to engineer the interface between hard and soft materials.

Highlights

Description of the unbiased array-based sensing method is presented.

Selective interactions of sensors allow detection of subtle variations on cell surfaces.

Unbiased array-based sensors have been used to discriminate cell states.

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Figure 1. Schematic presentation of gold nanoparticle based sensor array. Nanoparticle-fluorescent probe complexes, either fluorescent polymer or protein, are incubated with mammalian cells. Differential fluorescence recoveries are produced depending on nanoparticle functionality and cell surface. These can then be classified using linear discriminate analysis (LDA).

a) Depiction of chemiluminescence sensor array. Cells upon incubation with the catalysts generate distinct thermoluminescence responses. b) Clustering of cell lines using LDA. c) Structure of magnetic nanoparticles with carbohydrate functionalities. The carbohydrate moieties interact with the phenotypic receptor presentation on the cell surface. The reduction in transverse relaxation times can then be measured and statistically analyzed to differentiate cells. Reprinted with permission from reference 6, 7. Copyright 2011, 2010 American Chemical Society.