Journal of Bioanalysis & Biomedicine

Chandra, J Bioanal Biomed 2013, 5:5
DOI: 10.4172/1948-593X.1000e122

Editorial Open Access

Miniaturized Multiplex Electrochemical Biosensor in Clinical Bioanalysis

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Detection of a target molecule in environmental or clinical samples is extremely important and critical. There are ample of methods to diagnose or detect target molecule in various clinical samples. Methods based on genomic [1] and proteomic [2] assays using molecular methods are quite common and widely applicable all around the world. In clinical sample analysis usually either a protein biomarker [3, 4] (*eg*: human epidermal growth factor receptor 2 for breast cancer, prostate specific membrane antigen for prostate cancer) or a genetic biomarker [5] (*eg*: bone morphogenetic protein 3 gene for biliary cancer) is used to diagnose the occurrence or progression of a disease. Although a single biomarker can be used to diagnose a disease, but there are issues where a single biomarker alone cannot accurately predict occurrence of the disease [6]. To address this multi analyte detection various molecular methods have been developed such as; multiplex polymerase chain reaction analysis [7], multiplex ligation-dependent probe amplification [8], DNA microarray for gene expression or SNP detection assays [9], protein microarray [10], phage display [11] *etc*. These methods, however, are extremely powerful for multianalyte detection but they suffer due to their cost and inability of miniaturization for the onsite analysis. Furthermore, these methods require well qualified professionals for their real implementation in hospitals. Thus, in recent years a biosensor based multianayle detection of important clinical molecules have been attempted [12]. A biosensor is an analytical device used for the detection of a target molecule. It is composed of majorly two elements; a biological recognition element able to interact specifically with a target and a transducer able to convert the recognition event into a measurable signal [13]. Among the entire biosensor read out devices an electrochemical system method is usually preferred due to the advantages of being portable, simple, easy to use, cost-effective, disposable, and possible method for the lab-on-a-chip diagnostic system [14, 15]. The multiplex biosensors that are capable of detecting multiple targets has provided more accurate diagnosis and monitoring in recent times. This type of biosensor technology relies on multiple transducers that are independently targeted to a specific protein or antigen for detection. Since this technology is reliable, low cost, and simply scaled-down with the use of semiconductor materials, electrochemical-based biosensors have been key players in the area of multiplex biosensors [16-18]. The performance of the electrochemical biosensor has been shown for nucleic acid [19] and protein biomarker [20] detection. Apart from the biosensor based systems, microfluidic device integrated with either an external [21] or an integrated biosensor [22] have been very well implemented in the simultaneous detection of various clinically important target molecules such as; anticancer drugs [21], sulfonamides [23], endocrine disruptors [24], and heavy metal ions [22]. In this regard, Chandra et al. developed a simple and highly sensitive method for the multiplex detection of anticancer drugs in urine samples using an amperometric biosensor composed of double stranded DNA and cardiolipin coupled with a microfluidic device [21]. The detection limit of these drugs was in pM range and the developed method detected these drugs simultaneously without any interference. Since DNA molecule is an extremely important molecule to diagnose a medical disorder, electrochemical multiplex biosensor has been attempted by many workers for various biomarkers. For instance; a novel electrochemical DNA biosensor for detection of a pre-core mutation in the hepatitis B virus was developed by oligonucleotide attached onto a nonfouling surface. The developed multiplexing method was able to analyze 16-samples simultaneously [25]. In an another study of multiplex DNA detection, very recently a hairpin DNA probe mediated cascade signal amplification technique has been developed for the quick DNA detection with a detection limit of 100 aM [26]. The implementation of tag/anti-tag DNA and gold nanoparticles (NP's) reporters in this method allows a universal platform for the multiplex DNA detection without instrumentation. Apart of DNA molecules, proteins have also been detected by multiplex biosensor systems. In one example; an electrochemical immunosensor for detection of tumor markers has been developed. The biosensor consisted of an array of immunosensing electrodes fabricated on a glass substrate where each electrode was coated with a separate antigen and was able to make immuncomplex with a specific tumor marker [27]. This multiplexing biosensor was used to measure the concentrations of important tumor markers such as; alpha-fetoprotein, ferritin, carcinoembryonic antigen, human chorionic gonadotropin, CA 15-3, CA 125, and CA 19-9 with the detection limit of < 2 ng/mL. In another study, a multiplexed biosensor using rapid and label free electrochemical impedance spectroscopy tuning method has been developed for the detection of inflammatory markers. An off-chip conjugation of gold NP's to the molecular recognition elements has been very well explored in this case [28]. In a very recent study, a microfluidic paper-based electrochemical biosensor array (1 × 8) has been developed as a diagnostic test of multiple biomarkers in a multiplexing approach [29]. In this case a paper-based device and the potentiostat formed a convenient, integrated, easy-to-operate electrochemical biosensing platform, which is mainly useful for low-cost, point-of-care diagnostic applications. Three important metabolic biomarkers (glucose, lactate and uric acid) were analyzed simultaneously which shows lower or comparable detection values to the detection system present in the market indication the potential application of multiplexing. These examples clearly illustrates that a multiplex biosensor assays provide significant advantages over single-analyte tests in terms of cost per test, labor, miniaturized diagnostic, handling large sample number, and convenience. It is possible to anticipate that miniaturized biosensor such as; paper based multianalyte system described herein, could be extremely appropriate for the mass manufacturing which will be surely economical and can be applied in a wide range of clinical samples.

In conclusion, the miniaturized multiplexing biosensor have

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Received November 29, 2013; **Accepted** November 29, 2013; **Published** December 07, 2013

Citation: Chandra P (2013) Miniaturized Multiplex Electrochemical Biosensor in Clinical Bioanalysis. J Bioanal Biomed 5: e122. doi:10.4172/1948-593X.1000e122

reached long way and will continue to move forward quickly in the next decade, with involvement of large number of companies into research and development. The principle platform and concern will be one offering high-throughput, rapid, and low cost diagnostics.

Acknowledgement

Pranjal Chandra thanks Amity University Uttar Pradesh, Noida, India for providing the research facility.

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