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Advance Diagnosis of Drug Resistance in Cancer: Towards Point-of-Care Electronic Nanodevice

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Editorial

The development of multidrug resistance (MDR) in cancer cells is the main reason of cancer chemotherapy failure. Numerous mechanisms have been found which are responsible in the development of MDR in cancer cells [1]. The most important and well-studied factor responsible for is MDR, is a cell membrane transporter "permeability glycoprotein, (P-gp)" which is encoded by the MDR1 gene. P-gp possesses two membrane-spanning domains and two nucleotide-binding which work as energy dependent pump and reduces the transport of drug through the cell membrane. This results in low concentration of these drugs within the cells than the clinically relevant therapeutic levels [2,3]. This leads in the development of resistance in cancer cells towards drugs. In medical science it is extremely important to detect the onset of resistance in cancer cells which will be very helpful to design new therapeutic strategies to cure cancer patients. In the view of such an important clinical condition, numerous methods have been developed for the highly sensitive detection of these cancer cells. These methods include; polymerase chain reaction (PCR) [4], immunohistochemistry [5], flow cytometry [6], and microarray [7]. While these methods have been applied for the detection of drug resistant cancer cells (DRCC), but they are less sensitive, need extremely trained professionals, and lacks the ability to be miniaturized for the onsite medical detection. In recent years, electrochemical nanosensors are found to be the most promising approach to resolve the issues related to sensitivity, rapidity, selectivity, and ability to be miniaturized [8-17]. Thus, in biosensor-based detection technologies have been also attempted for the detection of DRCC. In this regard in mid-2000, Du et al., developed an electrochemical immunosensor for the detection of P-gp expressed on the K562/ADM l leukemic cells [18]. The detection signal was obtained due to the immunoreaction between P-gp monoclonal antibody and P-gp expressed cancer cells followed by the binding of secondary Alkaline Phosphatase (AP) conjugated antibody which catalyzes the reaction of 1-naphthyl phosphate to generate amperometric signals. The detection limit of this sensor was 1.0×10^4 cells/ml. In another study, an indirect nanosensor based method was developed to detect DRCC [19]. The main concept in this work was to monitor the uptake of anticancer drug by the cells. A carbon nanotube-glassy carbon nanosensor was developed and the uptake of anticancer drug, daunorubicin was monitored based on supramolecular interactions. The uptake of daunorubicin was monitored in terms of its direct electron transfer process. The method was very effective and was able to discriminate between DRCC and drug sensitive cancer cells. In another strategy, Zhang et al., developed a label free electrochemical nanosensor for detection of drug resistant leukemia K562/ADM cells based on P-gp expressions on the cell surface [20]. The detection was based on a nanosensor which was developed by immobilizing P-gp antibody onto a conducting polymer and gold nanoparticles composite. The interaction of the P-gp expressing leukemia cells with the sensor was monitored by electrochemical impedance spectroscopy, which is considered to be a label free method for bio-molecular detection. The sensor was very effective to detect DRCC up to 80 cells/ml, however, it was not applied to detect these cells in biological samples such as; blood and/or serum samples to evaluate its real clinical value. The latest and most sensitive sensor to detect DRCC has been developed by Chandra et al., and has ability to detect DRCC in biological matrix very effectively [21]. The overall sensor fabrication and its detection mechanism has been illustrated in Figure 1. The sensor was designed by immobilizing the P-gp antibody on highly conducting gold nanoparticles – conducting polymer composite developed in Yoon-Bo Shim's laboratory at Pusan National University, South Korea. A sandwiched type sensing format was adopted for the detection of DRCC where P-gp antibody served as a detector probe and aminophenol boronic acid attached with carbon nanotube and hydrazine served as a reported probe. The analytical signal was obtained due to the powerful electrocatalytic activity of hydrazine towards hydrogen peroxide reduction. An exponential range for the DRCC detection using this novel sensor was achieved between 50 and 100,000 cells/ml with the detection limit of 23 ± 2 cells/ml, which is the lowest value compared to any other DRCC sensor reported till date. The designed sensor was highly selective and was able detect the target cells in presence of drug sensitive and noncancerous cells and other chemical molecules present in the real sample environment. The clinical value of the sensor was examined by detecting DRCC in serum samples, and the results were very promising indicating its real biomedical value.

These studies clearly show that there are huge interest to develop highly sensitive point-of-care diagnostic methods to diagnose drug resistance in cancer cells. More research in this area will surely help the clinicians to design the appropriate therapeutic strategy which will reduce the pain of cancer patients and finally can be able to save their life. Future studies should be directed towards integrating these electronic nanosensors with microfluidic systems to develop a point-of-care nanodevice to address more precise issues related to drug resistance in cancer.

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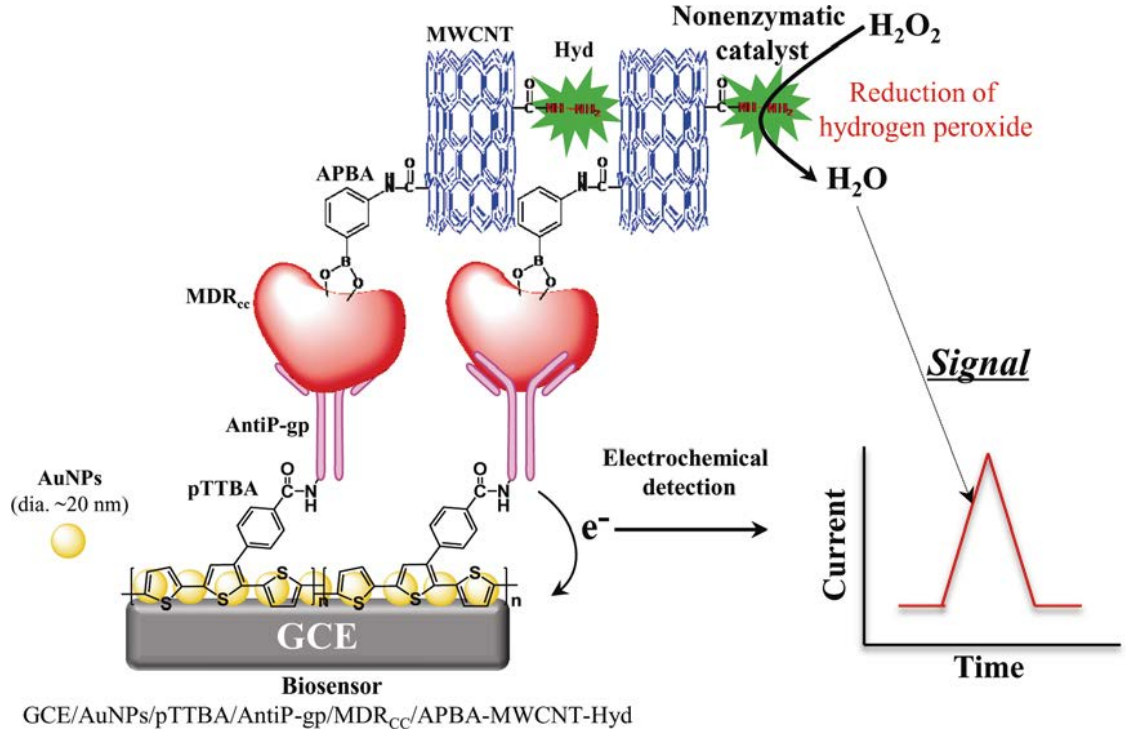

Figure 1: Schematic representation of the immunosensor fabrication and detection principle [reproduced with permission from reference number 21].

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