Editorial

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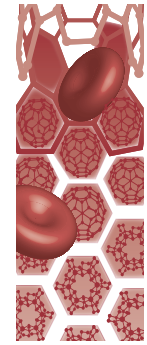

The carbon nanotube-based nanobiosensor: a key component for ubiquitous real-time bioscreening system?

"...a carbon nanotube-based nanobiosensor can be a possible solution to overcome the limitations of conventional biosensors and to enable a paradigm-shifting biosensor technology such as ubiquitous real-time nanobiosensors."

Keywords: carbon nanotube • nanobiosensor • nanomaterials • scalable biosensor • ubiquitous biodetection system

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Various biosensors have been utilized to detect specific biological molecules for quite versatile applications such as disease diagnostics, drug screening and bioterrorism prevention. One example is a glucose sensor that diabetes patients routinely utilize to check the glucose level in their blood. A common glucose sensor is comprised of electrochemical electrodes coated with glucose oxidase enzyme [1]. When the electrode is exposed to a patient's blood, the glucose oxidase enzyme oxidizes the glucose in the blood. The oxidation process generates electrons, which enables the current to flow through the electrode. Thus, by simply measuring the current levels, one can estimate the glucose level in the patient's blood [2]. Other examples of common biosensors might be strip-type biosensors for pregnancy tests and ELISA chips for an immune assay. Typical biosensors are comprised of three key components: a target, a sensing matrix and a sensor transducer. Here, the sensing matrix molecules selectively react with specific target molecules. Then, a sensor transducer device measures the reaction and generates electrical or optical sensor signals. In case of a glucose sensor, glucose, glucose oxidase enzyme and electrodes correspond to a target, a sensing matrix and a sensor transducer, respectively. The present biosensor market size is approximately US$13,000 million. A glucose sensor covers 85% out of the total biosensor market [3].

Recently, dramatic advances in nanotechnology and information technology have allowed one to envision new types of advanced biosensors, which could lead to a paradigm shift in modern biomedical industries. For example, one may be able to build a nanoscale real-time biosensor and combine it with a wireless communication device to build a ubiquitous real-time nanobiosensor. In this case, the nanobiosensor detects specific target biomolecules in real time and sends the sensing results immediately via wireless networks. Such real-time nanobiosensors with wireless communication can be utilized for various clinical and biomedical applications. For example, nanobiosensors can be utilized to build a convenient portable device for quick disease diagnostics and bioscreening, which may help to extend medical services into undeveloped rural areas. Another potential application could be implantable nanoscale biosensors that are implanted in a patient's body who suffers from a chronic disease and utilized to monitor the patient's health conditions in real time.

However, due to several fundamental limitations of conventional biosensor technology, it has been extremely difficult to realize such ubiquitous real-time nanobiosensors. For example, most of conventional biosensors require a labeling step, which is often time-consuming. In addition, the size scalability of conventional biosensors can be a problem. In the case of conventional biosensors, the reduction of the sensor size often results in a reduced sensor signal and, thus, a poor sensitivity. For example, glucose sensors with small electrodes can extract only a small amount of current signals because the measured currents are proportional to the electrode area. On the other hand, for some applications

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such as implantable health monitoring systems, one needs to use the same biosensor device repeatedly for a rather long time period. However, conventional biosensors are only meant for single usage, and they are not reusable. This is partly due to contamination from solution-based samples such as human blood or urine. In case of immunosensors based on antibody–antigen bindings, it is usually very difficult to remove antigen bound to antibody, which limits the repeated use of conventional biosensors.

> "Although carbon nanotubes or nanowire-based biosensors show great promise, it is also worth mentioning the major difficulties for their practical applications."

As a possible solution to overcome such limitations of conventional biosensors, we have been working on carbon nanotube-based biosensors. Carbon nanotubes (CNTs) are tube-like structures comprised of carbon atoms. The diameter of single-walled carbon nanotubes is a few nanometers, and its length can be as large as a few millimeters. Some carbon nanotubes can have a semiconducting property, and, thus, its electrical conductivities may be altered by external electrical fields. CNTs with semiconducting properties can be utilized as a sensor transducer device. For example, one can build electrical channels of CNTs between two electrodes and coat the carbon nanotube channels with the receptors for acetylcholine, a neurotransmitter, to build an acetylcholine sensor [4]. Here, when acetylcholine molecules bind to the receptor molecules on the CNTs, it changes the charging states of the acetylcholine–receptor molecule complex. Such change alters the electrical fields around the CNTs, resulting in an electrical current change in the CNT channels. Thus, simply by monitoring the current levels in the CNT channels, one can detect the acetylcholine. In this sensor, CNT channels between two electrodes work as a sensor transducer. Acetylcholine and acetylcholine receptor are a target and a sensor matrix, respectively. Significantly, the sensor responds to target molecules in real time without any labeling step. Such acetylcholine sensors may be interfaced with living tissue and utilized to selectively monitor acetylcholine generated by neural activities. Various biosensors can be built simply by coating CNT channels with different receptors. Examples include bioelectronic noses and tongues [5–8]. Due to the small diameter of a CNT, only a small amount of biomolecule can significantly alter the conductance of the CNT channels, and thus the biosensors based on CNTs can have a very high sensitivity. Such highly sensitive real-time nanobiosensors can also be built using nanowires instead of CNTs [9].

CNT-based nanobiosensors have an important advantage over conventional biosensors. First, since it is a label-free sensor, it can enable a real-time detection of specific biomolecules. Furthermore, CNT-based nanobiosensors can be scaled down without losing their signal size. The signal of a CNT-based biosensor is the electrical current between two electrodes through the CNT channel [10–12]. When the size of the sensor is reduced, both the width and length of the channels are reduced and, thus, the electrical current in the CNT channel remains the same. Note that conventional electrochemical biosensors such as glucose sensors exhibited reduced signals if the electrode size is reduced. We recently demonstrated CNT-based nanobiosensors even smaller than an individual cell [12]. The sensor has been inserted inside a Human Embryonic Kidney 293 cell (HEK-293 cell) and utilized to monitor the calcium ion concentration inside the cell. Similar semiconducting channel-based sensors can be built using nanowires and utilized for monitoring the response of individual cells [13].

On the other hand, there are also extensive efforts to develop reusable nanobiosensors. Duan *et al.* utilized supramolecular chemistry to build reusable nanobiosensors [9]. Here, silicon nanowire-based channels were functionalized with β-cyclodextrin (β-CD), to which receptor moieties can be attached with an orthogonal supramolecular linker. The devices were used to detect biotin–streptavidin interactions through small, orthogonal, multivalent linker molecules. After the first sensing, the bounded streptavidin and the linkers can be removed through competitive desorption with concentrated β-CD and a new β-CD layer was bound onto the nanowire surfaces, enabling the repeated application of sensors. Such a reusable biosensor may be one of the key technologies to enable various ubiquitous real-time nanobiosensor systems such as implantable health monitoring systems.

Although CNTs or nanowire-based biosensors show great promise, it is also worth mentioning the major difficulties for their practical applications. One of the most challenging problems of CNT-based biosensor technology has been its reliability. When CNTs are first synthesized, they are usually comprised of one-third metallic CNTs and two-thirds semiconducting CNTs. The properties of synthesized CNTs vary from a batch to batch. Thus, the characteristics of nanobiosensors based on such CNT materials can vary significantly, often resulting in unreliable sensor signals. Recently, significant progress has been made in improving the reliability of CNT-based biosensors. For example, Hersam *et al.* developed a method to purify CNTs and obtain only pure semiconducting CNTs

[14]. Furthermore, we reported a method to calibrate CNT-based sensor signals to obtain reliable sensing results [15].

In summary, a CNT-based nanobiosensor can be a possible solution to overcome the limitations of conventional biosensors and to enable a paradigm-shifting biosensor technology such as ubiquitous real-time nanobiosensors. It also shows us a new paradigm in the future biosensor research activities. Until now, most biosensor research has mainly focused on improving its sensitivity. However, for a new paradigm-shifting biosensor technology, one should pay attention to different aspects of CNT-based nanobiosensors such as sensing speed, scalability and reusability. Our group's research will also focus on these aspects of nanobiosensors and explore the new area of biosensor technologies.

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