MRS Communications

Introduction

Two-dimensional nanomaterials for healthcare and lab-on-a-chip devices

Venkatesan Renugopalakrishnan, Northeastern University and Harvard Medical School, Boston, MA, USA
Tharangattu N. Narayanan, Tata Institute of Fundamental Research, Hyderabad, India
Sakthi D. Kumar, Graduate School of Interdisciplinary New Science, Toyo University, Kawagoe, Saitama Prefecture, Japan
Yogish C. Kudwa, Mayo Clinic, Rochester, MN, USA
Jairam R. Eswara, Brigham and Women's Hospital, Boston, MA, USA

Recent years have witnessed the inroad of nanotechnology on healthcare, heralding a new era of nanomedicine. Recent research has covered the interface between materials and medical sciences: carbon-based nanomaterials and soft nanostructured biomaterials, such as proteins, enzymes, DNA, RNA, and viruses. Novel properties that differentiate nanomaterials from bulk materials generally develop at a length scale of ~10 nm. However, the size at which materials display different properties to the bulk material is material-dependent. From the biologic point of view, nanomaterials match the typical size of naturally occurring functional units or components of living organisms and, for this reason, enable more effective interaction with biologic systems. Further integration of two-dimensional (2D) nanomaterials and soft materials confer the specific functionalities of biologic macromolecules. Optimal application of nanomaterials in medicine to enhance quality-of-life outcomes can be understood from state-of-the-art knowledge on the nanoscale features of biologic systems in order to learn how to design nano-devices for biomedical uses. Nanomaterials have a relatively larger surface area and, therefore, are more chemically reactive. In addition, the nanoscale has a marked effect on the strength and electrical properties as the quantum effects dominate the behavior of materials with respect to their optical, electrical, and magnetic properties. Basically, nanomaterials fall into three categories: one- (1D), two- (2D), and three-dimensions (3D). Nanomaterials have been proposed as key components in biosensing, imaging, and drug-delivery schemes since they confer distinctive advantages over conventional approaches, e.g., sensitivity. In particular, the characteristic electronic and optical properties of carbon-based materials are potentially significant in diagnostic sensing and imaging in vitro and in vivo. The unique chemical and physical properties of carbon nanomaterials offer opportunities to functionalize and append biomaterials in developing protein transducers, therapeutic drug-delivery vehicles, gene-delivery systems, and microbial diagnostic, bacteria and viruses, for use in both in vitro and in vivo modes. These opportunities are transformative in healthcare, as we enter an era of personalized precision medicine, diagnostics, and theranostics.

In this issue, Des Brennan and Paul Galvin review flexible substrate systems (paper, polymer, and fabric) upon which multiplex biomarker assays are implemented. Such materials naturally conform to patient movement, offering potential for real-time patient monitoring in health and wellness applications. Approaches to sensor integration, sample collection, and assay implementation, enhancing selective biomarker detection over clinically relevant ranges are discussed. The review concludes by summarizing relevant technology trends, challenges, and future opportunities.

Vivekanandan et al. review multi-OOC as a solid platform that promises to deliver the ambitious dream of the "body-on-a-chip," rather "homo-chippiens." However, multi-OOC may lack the morphology of native organs, and subcutaneous implants are likely to face rejection. Multi-OCC as an external patch connected to mobile devices, however, is likely to be approved by the FDA. Researchers have made significant contributions to the development of OOC platforms in the past decade. However, biologic and technical challenges need to be addressed to ensure scaling this technology to the next level. Moreover, researchers must find a realistic way to transfer this technology from lab to market. Given the immense popularity and potential of OOC platforms to precisely predict the fate of drugs in human body, it can be a commercial drug testing platform and may be well-suited to replace the current animal-based modeling methods.

Ramasamy Paulmurugan et al. discuss the use of reduced graphene oxide (rGO) as a potential nanomaterial for quantification of microRNAs, including the structural differentiation of microRNAs in vitro in solution and inside intact cells. These were able to quantitatively differentiate intracellular single stranded miR-21 and miR-21–antimiR-21 hybrid within intact cells, which is difficult in using conventional assay systems. Finally, this study also showed the use of single-layer graphene placed on a silicon-oxide dielectric insulator as a sensor to differentiate single-stranded miRNA-21 from miRNA-21–antimiRNA-21 hybrid by electrical impedance spectroscopy assessment. Overall, the results of this study provide evidence for the potential use of graphene nanomaterials as a platform for

developing devices that can be used as microRNA quantitation sensors of biomarkers for clinical applications.

Shine Augustine et al. report the results of their studies relating to the application of 1D-MoO$_3$ for breast cancer detection. 1-D nanostructured MoO$_3$ have been synthesized via a simple one-pot hydrothermal approach. The higher electrocatalytic activity and mesoporous behavior of 1D MoO$_3$ provide a high aspect ratio for improved bimolecular loading. The developed 1D MoO$_3$-based immunosensor can efficiently and rapidly detect the HER-2 biomarker in the serum sample of breast cancer patients over other existing techniques. The fabricated immunosensor (BSA/anti-HER-2/APTES/nMoO$_3$/ITO) exhibits remarkable sensitivity (0.904 µA mL/mg/cm^2) and an improved LOD (2.47 ng/mL) toward the detection of the breast cancer biomarker (HER-2). This emerging 1-D nMoO$_3$ may be utilized toward the application in biomolecular electronics, biofuel cells, therapeutics, and detection of other biomarkers released in communicable and other non-communicable diseases.

Usunoglu et al. discuss how the unique properties of (2D) rGO and (1D) MWCNTs were successfully extended to 3D by exploiting the synergetic effect between rGO and MWCNTs to design novel electrocatalysts for electrochemical sensing. It was seen that the introduction of MWCNTs into the catalyst layer besides rGO enhanced the electrochemical performance of the sensors significantly toward H$_2$O$_2$.

Jasper et al. discuss graphene-based electronic DNA sequencing devices which have the potential to bring significant advances in modern healthcare by providing inexpensive portability. However, DNA sequencing is yet to be demonstrated using these devices, largely due to their complex fabrication requirements. This paper reviews the general fabrication principles of graphene-based electronic DNA sequencing devices, as well as highlighting common fabrication challenges and their potential solutions.

In "Nickel-reduced graphene oxide composite foams for electrochemical oxidation processes: towards biomolecule sensing," Thoufeeq et al. report on the possibilities of thermally deduced graphene (rGO)-protected metallic sponges (here nickel sponge) for biomolecule sensing applications. An oxidative sensing process such as non-enzymatic glucose sensing is carried out where the Ni–rGO composite foam is found to be outperforming the bare metallic sponge. This sensing capability of the composite sponge is extended to methanol oxidation, too. The method reported here is also adoptable for Ni–graphene-based ink development for printable devices, opening new avenues in developing graphene-protected metallic electrode-based high sensitivity sensors and devices.

Liu, Meng et al. discuss how sensitive detection of *Escherichia coli* can be achieved via a simple biosensor made of GO non-covalently adsorbed with an *E. coli* responsive catalytic DNA (DNAzyme). This strategy should be generally applicable for the detection of any pathogen of interest as long as there is an available DNAzyme for the pathogen.

Diabetes continues to be a widely prevalent and challenging disease to accurately diagnose and manage. The burden is increasing as patients are living longer. Frequent non-invasive glucose sensing needs to be an integral part of treating any diabetes that requires more than oral medications. The regimen used presently involves frequent, painful, finger-pricks, and can be a deterrent to patients, especially in a neonatal pediatric setting. A non-invasive method of testing would encourage more patients to engage in monitoring. In addition, it would allow more frequent testing which would result in tighter glucose control with the likelihood of better long-term outcomes. Current technology for non-invasive frequent sensing of glucose, though much improved, is not sufficiently miniaturized and carries significant burden to the patient. Thus, enhanced graphene-based glucose, insulin, and glucagon sensing is critical in monitoring and managing diabetes.

An artificial "pancreas-on-a-chip" (Vivekanandan et al.) designed around a multiplex sensor *sans* its natural habitat would mimic the function of a real pancreas. The pancreas is an organ that secretes several hormones, including insulin and glucagon, as well as digestive enzymes that help breakdown food. Insulin helps cells in the body to take up glucose from the blood to use for energy transduction which lowers blood glucose levels, and glucagon causes the liver to release stored glucose which raises blood glucose levels. An artificial pancreas might be built from a multiplex of point-of-care devices mimicking the functionality of the pancreas better than a single analyte glucose sensor, extendible to other organs. Whole-organ pancreas transplantation, either alone or combined with a kidney transplant, is the only ultimate treatment for many patients with type-1 diabetes to restore normal glucose homeostasis and insulin tolerance, and hence an artificial pancreas is the closest approximation to whole pancreas transplant.

This special issue includes some of the current advances in the rapidly emerging interface of 2D nanomaterials in the design of point-of-care devices/biosensors.