News & Views in ...
Nanomedicine
Highlighting the latest news in nanomedicine

Novel biosensor may be an important step towards diagnosing early-stage Parkinson's disease

ZnO nanowire/graphene foam electrode is capable of detecting low levels of uric acid in patients with Parkinson's disease.

Researchers from Sungkyunkwan University (Republic of Korea), in collaboration with Harbin University of Science and Technology (China) and Chungnam National University Hospital (Republic of Korea), have reported on the development of a novel biosensor capable of detecting biomarkers associated with Parkinson's disease (PD), potentially representing a significant advance towards diagnosing PD in its early stages.

The study describes the fabrication of vertically aligned ZnO nanowire arrays on 3D graphene foam, which was used to selectively detect uric acid (UA), dopamine (DA) and ascorbic acid (AA) by a differential pulse voltammetry method.

Speaking to *Nanomedicine,* lead researcher Young Hee Lee, from Sungkyunkwan University, explained that low levels of DA are strongly linked to neurological disorders such as PD and schizophrenia. Since DA coexists with UA and AA in serum and the extracellular fluid of the CNS, Lee commented that, using conventional solid electrodes, "it is difficult to simultaneously detect DA, UA and AA in a mixture with high selectivity and sensitivity due to overlapping oxidation potentials, insufficient surface area and/or the limited kinetic accessibility of each species."

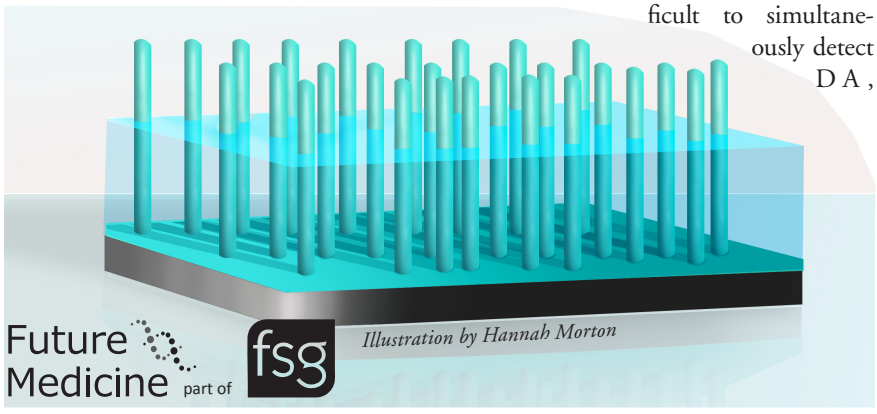

Illustration by Hannah Morton

According to the study, the optimized ZnO nanowire/graphene foam electrode provided a high surface area and high selectivity with a detection limit of 1 nM for UA and DA. Lee commented that the "key features of our structural design are a large surface area with mesoporous 3D graphene structures to facilitate ion diffusion easily; high conductivity from 3D graphene foam; and active sites of ZnO surface for high selectivity."

In order to carry out the analysis, serum was extracted from human peripheral blood of healthy individuals, in addition to PD patients. This process involved proton and electron generation at the surface of the ZnO nanowire arrays, causing the transfer of electrons to the electrode. Using differential pulse voltammetry measurements with the ZnO nanowire/graphene foam electrode, the samples were analyzed for UA levels. The average UA concentrations for the healthy individuals and the PD patients were 355 ± 30 and 265 ± 20 μM, respectively. According to Lee, "this clear reduction in UA levels in the serum of PD patients with reliable statistics ($p < 0.001$) strongly implies that our approach is a significant step forward, which we believe will be beneficial for diagnosing PD and monitoring disease progression."

Currently, diagnosis of PD essentially relies on the assessment of clinical symptoms and a blood test for PD is a major goal for researchers. Speaking to *Nanomedicine* about the

significance of the study, Lee commented that, "being able to accurately test for biomarkers associated with the disease with simple blood tests would be a major breakthrough in diagnosing PD in the early stages when treatments are most likely to be effective."

In terms of future work the team intends to improve on the electrode design in order to achieve the simultaneous and accurate detection of other disease biomarkers and biomolecules. Lee added that, "Since the oxidation potential of some biomolecules may overlap, there is no guarantee that they can always succeed. Therefore, we will proceed by testing individual diseases, including cancers, in order to improve their sensor design and make it as generally applicable as possible."

– Written by Hannah Coaker

Source: Yue HY, Huang S, Chang J et al. *ZnO nanowire arrays on 3D hierachical graphene foam: biomarker detection of Parkinson's disease.* ACS Nano *doi:10.1021/nn405961p (2014) (Epub ahead of print).*

Delivery of siRNA packages

A team of researchers at Vanderbilt University (TN, USA) have developed a biodegradable nano-scaffold that can deliver siRNA to cells, in order to promote blood vessel growth and tissue regeneration, therefore hoping to provide a new approach for the treatment of chronic wounds. The siRNA was packaged inside nanoparticles to protect the fragile genetic material that would usually denature under normal conditions.

The addition of the pore-creating compound trehalose enabled implantation under the skin and release at a variety of speeds over several weeks. During the study, a mouse was implanted with the scaffold in order to knock down the gene *PHD2* that inhibits the growth of blood vessels. It was found that the delivery of siRNA using the scaffold over 33 days increased the local blood vessel volume by threefold.

Craig Duvall, who led the study, commented on the adaptability of this development, "Depending on the target gene, and its time course of expression during the wound-healing process, you may want to have a fast, short-lived silencing effect, or you may want to have a long-term, sustained silencing effect. For example, in a hard to close wound, you may want to deliver siRNA for a month, or even longer. With this scaffold, we can make that adjustment by simply tuning the quantity of trehalose."

The next step for the team is to test the efficacy of the nano-scaffold in diabetic rats (as diabetic patients are at more risk of developing chronic wounds) and explore the targeting of different types of genes using siRNA treatment. Duvall hopes that the scaffold will be brought to the clinic in 5 years.

– Written by Lisa Parks

Sources: Nelson C, Kim A, Adolph E. Tunable delivery of siRNA from a biodegradable scaffold to promote angiogenesis in vivo. Adv. Mater. *26(4), 607–614 (2014); Breakthrough technology enables gene silencing to heal wounds: www.nibib.nih.gov/news-events/newsroom/breakthrough-technology-enables-gene-silencing-heal-wounds*

High-density lipoproteins may offer a more promising route to statin therapy

In a collaborative effort, researchers have developed an injectectable reconstituted high-density lipoprotein (HDL) nanoparticle carrier vehicle capable of delivering statins to treat atherosclerotic plaque inflammation.

Although statins have potent anti-inflammatory properties, they suffer from low systemic bioavailability if administered by the conventional oral route, thereby reducing the overall effectiveness of this therapy.

By formulating synthetic versions of HDLs, a key component in the transportation of molecules such as cholesterol and fats in the body, the team was able to successfully deliver anti-inflammatory drugs to the heart, potentially enabling the prevention of repeat heart attacks or stroke.

The group demonstrated the effectiveness of this approach with two different treatment regimens in an apolipoprotein E-knockout mouse model of atherosclerosis. Leader of the study, Willem Mulder, a researcher at Mount Sinai School of Medicine (NY, USA), commented, "A 3-month low-dose nanotherapy regimen was found to inhibit plaque inflammation progression, while a 1-week high dose lowered inflammation bur-

den by 90% in advanced in advanced atherosclerotic lesions."

In terms of the current standard of care, recurrence rates after myocardial infarction or stroke are as high as 30%. With this in mind, Mulder concluded that, "this novel approach represents an alternative and effective treatment paradigm for atherosclerotic disease, which may be employed to swiftly stabilize subjects and reduce the high recurrence rates."

With regard to future work, the team now intends to evaluate the HDL statin nanotherapy in more clinically relevant animal models, in addition to investigating the incorporation of different anti-inflammatory compounds to potentially achieve a more potent formulation. According to Mulder, "The group's ultimate ambition is to perform trials with our clinical partners at the Academic Medical Center in Amsterdam (The Netherlands)."

– Written by Hannah Coaker

Source: Duivenvoorden R, Tang J, Cormode DP et al. *A statin-loaded reconstituted high-density lipoprotein nanoparticle inhibits atherosclerotic plaque inflammation.* Nat. Commun. *doi:10.1038/ncomms4065 (2014) (Epub ahead of print).*

Immune-modifying microparticles – a possible therapy for inflammatory disease?

A group of researchers has reported on the modulation of inflammatory monocytes by immune-modifying microparticles (IMPs). Such monocytes are known to play an important role in the pathogenesis of numerous inflammatory diseases, such as multiple sclerosis, inflammatory bowel disease, transplantation reperfusion injury and infectious diseases where inflammatory macrophages are a consistent and significant component.

In the study, the team demonstrated that infused negatively charged IMPs, derived from polystyrene, microdiamonds, or biodegradable poly(lactic-*co*-glycolic) acid, were taken up by inflammatory monocytes via the macrophage receptor with collagenous structure. Subsequently, it was discovered that these monocytes no longer trafficked to sites of inflammation, but instead IMP infusion caused their sequestration in the spleen.

The team administered IMPs in mouse models of myocardial infarction, experimental autoimmune encephalomyelitis, dextran sodium sulfate–induced colitis, thioglycollate-induced peritonitis and lethal flavivirus encephalitis. The results indicated that the IMPS achieved a marked reduction in monocyte accumulation at inflammatory foci and disease symptoms, in addition to promoting tissue repair.

Speaking to *Nanomedicine*, Nicholas King, a researcher at the University of Sydney (Australia) who co-led the project, described the findings as significant: "to date, no approach exists that can specifically target the inflammatory monocyte population responsible for the tissue damage in a heart attack."

King further commented: "Moreover, our approach makes use of a natural dead cell disposal pathway and since many diseases are based on inflammatory monocytes that infiltrate tissues to become inflammatory macrophages and do significant damage, this approach could be used to reduce tissue damage and symptoms in several other such diseases."

The team now plans Phase I and II trials, initially targeting myocardial infarction, as well as a project with collaborators in Nepal with the aim of applying the approach in acute encephalitis syndrome, which is caused by flavivirus encephalitis in humans.

"The team intends to investigate in greater detail the mechanism of action of this intervention to see if the efficacy can be further enhanced, as well as extending into other macrophage disease models," said King.

– Written by Hannah Coaker

Source: Getts DR, Terry RL, Getts MT et al. *Therapeutic inflammatory monocyte modulation using immune-modifying microparticles.* Sci. Transl. Med. *6(219), 219ra7 (2014).*