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Previews

Sensitive, Rapid, Low-Cost, and Multiplexed COVID-19 Monitoring by the Wireless Telemedicine Platform

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To prevent the more severe spread of COVID-19 infections, sensitive, rapid, low-cost, and multiplexed detection is critical. Recently, Gao et al. reported a laser-engraved graphene-based wireless device to monitor multiple biomarkers from human biofluids, allowing for high-frequency self-testing of COVID-19 with high accuracy and low cost.

According to the data collected by the WHO, SARS-CoV-2 induced a higher case fatality rate (around 3.3%) than that of the previous influenza pandemics in 1918 and 1957,¹ and its spread rate is even 40-fold higher than that of SARS-CoV.² Until now, the collaboration of multidisciplinary scientists has promoted coordinated treatment and vaccination strategies, but risks associated with COVID-19 are not mitigated. To achieve a safe re-opening of society, the economy, and college campuses, accurate, rapid, and low-cost detection strategies are critical to hinder the transmission of SARS-CoV-2.^{3,4}

While it is readily clear that symptomatic individuals require identification in order to reduce community spread, asymptomatic persons should also be monitored. Real-time polymerase chain reaction (RT-PCR) on the virus nucleic acid is regarded as the current golden standard testing approach, though its drawbacks include expensive equipment, the need for professional technicians, being time-consuming, and as-known false negatives. These drawbacks restrict its potential use in daily self-testing.^{5,6} Besides, determinations of an individual's serologic status regarding antibodies specific to the vi-

rus antigens and circulating inflammatory biomarkers are equally important on identifying convalescent persons and evaluating COVID-19 severities.³ Therefore, a highly sensitive, rapid, low-cost, and multiplexed COVID-19 test is still highly demanded.

Emerging two-dimensional (2D) mono-elemental materials (Xenes) have shown a great potential in multiple biomedical applications including monitoring and detection of various diseases.⁷ As one of the most representative Xenes, the use of graphene in this specific field is very attractive. For example, in previous works, Gao et al. provided a wearable, inexpensive, and possibly scalable biosensing strategy based on mesoporous graphene electrodes made by CO₂ laser engraving.^{8,9} The graphene-based biosensor enabled rapid, accurate, multiplexed, and wireless monitoring of tyrosine (Tyr) as well as uric acid (UA) at low concentrations in human perspiration.⁸ The satisfied carrier mobility, significant electron transfer rate, and large surface area endow graphene with outstanding electrochemical properties, particularly appropriate for constructing biosensors to probe electroactive analytes at ultra-low concentrations in body fluids.^{8–10} The detection limits of the biosensors

to UA and Tyr were down to 0.74 μM and 3.6 μM , respectively.⁸ It is believed that the laser-engraved graphene-based biosensing device with high sensitivity, low-cost, and rapid detection ability to probe biomarkers from human biofluids will promote its potential clinical application.

With these solid foundations, Gao et al. recently demonstrated a wireless multiplexed electrochemical device to monitor COVID-19 with the features of low in price, high sensitivity, and rapidity, as named SARS-CoV-2 Rapid-Plex (Figure 1).³ The device could detect not only the viral antigen, immunoglobulins, but also the inflammatory biomarker, which represents three main COVID-19 aspects including the infection of virus, immunoreaction, and severity of clinical symptoms. This device contained four working electrodes and one counter electrode that were made of graphene, together with one Ag/AgCl reference electrode. All the electrodes were patterned by laser engraving on a polymeric substrate, which enabled its mass, low-cost production for wide application in the community. Instead of direct functionalization on graphene that generally requires a defected surface structure, 1-pyrenebutyric acid (PBA) was conjugated on the graphene sheet surface via π - π stacking and hydrophobic interaction, which was further utilized for binding the capturing receptors on the working electrodes. Immobilization of specific receptors including

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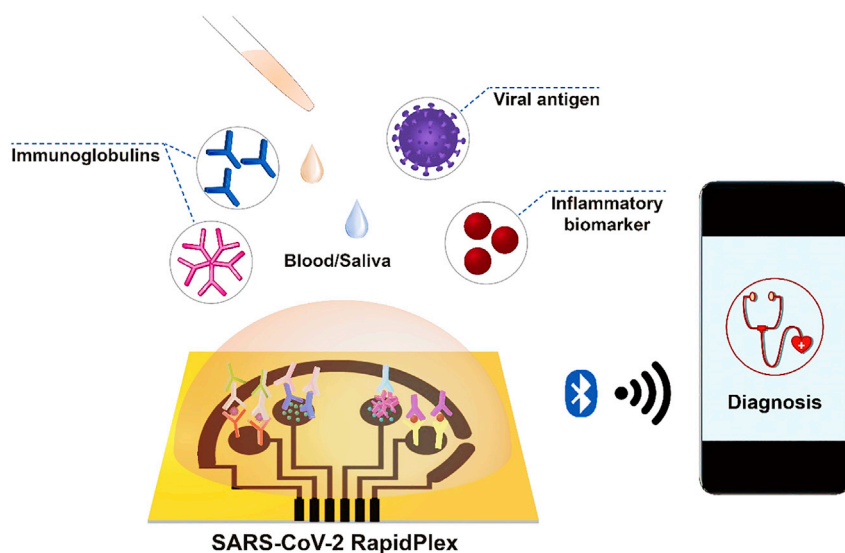


Figure 1. Sensitive, Rapid, Low-Cost and Multiplexed COVID-19 Monitoring by the Wireless Telemedicine Platform

nucleocapsid protein (NP), immunoglobulins against spike protein of the virus (S1-IgG, S1-IgM), and C-reactive protein (CRP) relied on covalently bonding their amino groups with carboxylic groups in PBA. In this way, the graphene maintained its initial structure and functionalities, ensuring good stability of the sensing layer. Besides, the presence of PBA together with an optimal blocking process by bovine serum albumin (BSA) also contributed to preventing non-specific adsorptions of large biomolecules on the graphene surface. The detection of each target biomolecules was visualized through comparing the amperometric signals in the absence and after binding of target analytes on each graphene working electrode, and the data could be wirelessly transmitted to a remote device over Bluetooth.

Aiming for an urgently needed fast-detection platform for COVID-19, the target binding time greatly determines its implementation potential. By comparing the amperometric signals from each sensing unit after incubating with blank and target samples (low to 500 pg/mL), a significant change was quickly observed within 1 min of incu-

bation. Notably, to ensure reliable sensitivity for detecting each target molecule at an ultra-low concentration, the incubation was recommended to perform for 10 min. Unlike other determination approaches based on either ELISA test, nucleic acid amplification, or mass spectrometry that is mostly hindered by complex sample preparation, high-cost, or bulky systems, the short-to-answer time endowed the as-developed device more implementation potential as a point-of-care (POC) system.³ Relative standard deviation (RSD) analysis on the response of different batch biosensors presented good reproducibility in terms of the fabrication process and signal transduction. Even after 5-days storage at 4°C, the detection performance showed negligible fluctuation. In the selectivity evaluation of the SARS-CoV-2 RapidPlex platform, no significant cross-reaction between the SARS-CoV-2 biomarker and that of interferents (non-target molecules) such as SARS and MERS coronaviruses was realized. More importantly, Gao et al. verified that there's no mutual interference between the readout from neighboring working electrodes when buffered solutions containing all the targets were

applied, i.e., 1 ng/mL of NP antigen, 250 ng/mL of S1 specific IgG and IgM, and 50 ng/mL of CRP.

To evaluate the clinical potential of this multiplexed platform, Gao et al. performed detections on both COVID-19-positive and COVID-19-negative blood/saliva samples from healthy individuals and confirmed patients. The device was able to simultaneously provide a positive readout for each individual target molecule after 1 min incubation with the COVID-19 positive serum samples. The signal-to-blank ratios representing the signal changes were 10.53 for NP, 11.62 for S1-IgG, 10.67 for S1-IgM, and 12.39 for CRP in serum samples, respectively, while the corresponding values were 2.81, 3.24, 1.62, and 1.76 in saliva samples.³ In the test on patient biospecimens, concentrations of the four biomarkers detected by the device were in the range of sub-micro- to micro-gram per milliliter in serum samples, and a range down to nanogram per milliliter in saliva samples. The positive readings of the biomarkers in patients' saliva supported the non-invasive diagnosis approach of SARS-CoV-2 infection from this biofluid. Moreover, through CRP concentration evaluation, various COVID-19 symptom severity grades could be determined, which would benefit the efficient allocation of medical attention and precious resources.

Overall, this study presents a novel wireless electrochemical platform of SARS-CoV-2 RapidPlex, aiming to accurately, rapidly, and inexpensively detect COVID-19 through the simultaneously multiplex test of NP antigen, S1-specific IgG and IgM, and CRP in serum/saliva. Further studies concerning large-scale clinical tests are still needed to verify the reliability of the biosensors before its real implementation as an efficient POC system contributing to fighting this COVID-19 pandemic. Further technological improvement may rely on the

integration of an automated microfluidic module for handling samples, and probably wearable biosensors for continuously monitoring an individual's health status against the COVID-19 infection.

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Give Life to a Glue

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Engineered living materials (ELMs), with the potential to recapitulate the autonomous and even intelligent biological systems, are gaining traction with synthetic biologists. The Zhong group reported the creation of living glues—a prototype of intelligent ELMs—enabling autonomous repairs.

Materials science has long been a duet of organic and inorganic matters, but has paid little attention to the possibilities rendered by diverse biological systems. Recently, the marriage of synthetic biology and materials science has given birth to the concept of engineered living materials (ELMs)—a new category of materials that possess some hallmark features of life, such as

self-replication, self-regeneration, environmental responsiveness, evolvability, autonomy, and perhaps even intelligence. However, the previously reported ELMs are quite primitive, mostly comprising a simple blend of engineered living cells and synthetic motifs. Sophisticated “living” features such as autonomy and intelligence remain elusive for ELMs, especially when com-

plex real-world test scenarios are concerned.

Bacterial biofilms are characterized by 3D polymeric extracellular matrices embedded with living cells. These naturally occurring living materials, the *Escherichia coli* biofilm in particular, have provided an important source of inspiration for synthetic biologists in recent years. For instance, CsgA, a

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