Bioconjugated Nanomaterial for Targeted Diagnosis of SARS-CoV-2
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CONSENSPECTUS: Infectious diseases by pathogenic microorganisms are one of the leading causes of mortality worldwide. Healthcare and socio-economic development have been seriously affected for different civilizations because of bacterial and viral infections. According to the Centers for Disease Control and Prevention (CDC), pandemic in 1918 by the Influenza A virus of the H1N1 subtype was responsible for 50 to 100 million deaths worldwide. Similarly, the Asian flu pandemic in 1957, Hong Kong flu in 1968, and H1N1pdm09 flu pandemic in 2009 were responsible for more than 1 million deaths across the globe each time. As per the World Health Organization (WHO), the current pandemic by coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is responsible for more than 4.8 M death worldwide until now. Since the gold standard polymerase chain reaction (PCR) test is more time-consuming, the health care system cannot test all symptomatic and asymptomatic Covid patients every day, which is extremely important to tackle the outbreak. One of the significant challenges during the current pandemic is developing mass testing tools, which is critical to control the virus spread in the community. Therefore, it is highly desirable to develop advanced material-based approaches that can provide a rapid and accurate diagnosis of COVID-19, which will have the capability to save millions of human lives.

Aiming for the targeted diagnosis of deadly virus, researchers have developed nanomaterials with various sizes, shapes, and dimensions. These nanomaterials have been used to identify biomolecules via unique optical, electrical, magnetic, structural, and functional properties, which are lacking in other materials. Despite significant progress, nanomaterial-based diagnosis of biomolecules is still facing several obstacles due to low targeting efficiency and nonspecific interactions. To overcome these problems, the bioconjugated nanoparticle has been designed with surface coating with polyethylene glycol (PEG) and then conjugated with antibodies, DNA, RNA, or peptide aptamers. Therefore, the current Account summarizes an overview of the recent advances in the design of bioconjugated nanomaterial-based approaches as effective diagnosis of the SARS-CoV-2 virus and the SARS-CoV-2 viral RNA, antigen, or antibody, with a particular focus on our work and other’s work related to this subject. First, we present how to tailor the surface functionalities of nanomaterials to achieve bioconjugated material for targeted diagnosis of the virus. Then we review the very recent advances in the design of antibody/aptamer/peptide conjugated nanostructure, which represent a powerful platform for naked-eye colorimetric detection via plasmonic nanoparticles. We then discuss nanomaterial-based surface-enhanced Raman scattering (SERS) spectroscopy, which has the capability for very low-level fingerprint identification of virus, antigen, and antibody via graphene, plasmonic nanoparticle, and heterostructure material. After that, we summarized about fluorescence and nanoparticle surface energy transfer (NSET)-based on specific identification of SARS-CoV-2 infections via CNT, quantum dots (QDs), and plasmonic nanoparticles. Finally, we highlight the merit and significant challenges of nanostructure-based tools in infectious diseases diagnosis. For the researchers who want to engage in the new development of bioconjugated material for our survival from the current and future pandemics, we hope that this Account will be helpful for generating ideas that are scientifically stimulating and practically challenging.

1. INTRODUCTION

Over the centuries infectious diseases caused by deadly viruses, bacteria, and different organisms have been among the leading causes of mortality in this world.1−3 Around 103 years ago, the 1918 influenza pandemic, infected 500 million people worldwide and killed more than a half-million people in the United States and up to 50 million people worldwide.1−3 The acquired immunodeficiency syndrome (AIDS) epidemic started 40 years before, has killed more than 35 million people until today.1−3 As of March 2020, the world is currently dealing with a global outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.4−8 The current pandemic

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has taken more than 4.2 M human lives worldwide until now. It has also created vast volatility, uncertainty, and complexity in healthcare, education, transportation, and the financial industry in our world. The current pandemic has highlighted the massive need for rapid and accurate diagnosis to control the spread of the virus by quarantining. The current diagnosis techniques used in clinics for COVID-19 infections are reverse-transcription polymerase chain reaction (RT-PCR), reverse-transcription loop-mediated isothermal amplification (RT-LAMP), clustered, regularly interspaced short palindromic repeats (CRISPR), enzyme-linked immunosorbent assay (ELISA), lateral flow assay (LFA), etc. (Figure 1). The gold standard real-time polymerase chain reaction (RT-PCR), which targets different SARS-CoV-2 genomic regions such as nucleocapsid (N), spike (S) protein, or envelope (E) genes is the ultimate diagnostic method for the detection of SARS-CoV-2 (Figure 1). Since PCR procedures need 1–3 days to confirm the clinical data, clinicians cannot perform millions of tests per day, which is extremely important to control the outbreak. Therefore, there is strong demand for the development of rapid diagnostic tests, which can have high sensitivity and specificity for

Figure 1. Current diagnostics methods for SARS-CoV-2 used in clinics. Reproduced with permission from ref 8. Copyright 2021 American Chemical Society.

Figure 2. Schematic illustration of bioconjugated nanoscale material-based tools that have been designed to diagnose the SARS-CoV-2 RNA, antigen, and antibody. Reproduced with permission from ref 16. Copyright 2020 American Chemical Society. Reproduced with permission from ref 38. Copyright 2021 American Chemical Society. Reproduced with permission from ref 19. Copyright 2021 American Chemical Society. Reproduced with permission from ref 37. Copyright 2021 American Chemical Society.
measuring virus RNA, antigens (S or N protein), or antibodies (IgA, IgM, IgG) of symptomatic or asymptomatic patients.\(^{10-30}\) Clinical testing facilities need novel point of care (POC) devices that can provide results very rapidly, maybe within 5 min.

To overcome the problem, researchers have developed several nanomaterial-based approaches.\(^ {20-43}\) Since nanomaterials exhibit unique structural and functional properties, considerable efforts have been made in the last year on the rational design of nanoprobe to improve SARS-CoV-2 diagnosis (Figure 2).\(^ {10-30}\) For reported diagnosis tools, various unique optical and electrical properties of nanomaterials have been used for signal transduction.\(^ {20-40}\) Since mass testing is fundamental to tackle the COVID-19 pandemic, several efforts are currently underway to develop easy-to-use colorimetric diagnostic tests that can be used in point-of-care settings or even for home daily use kits.\(^ {15-24}\) Since plasmonic gold nanoparticles have several orders of magnitude higher extinction coefficients than common dyes, it has been used heavily for sensitive colorimetric diagnosis purpose.\(^ {15-24}\) Similarly, high sensitivity and single molecular level detection capability diagnosis tools such as surface-enhanced Raman spectroscopy (SERS) and nanomaterial-based surface energy transfer (NSET) have been developed using nanomaterials.\(^ {23-35}\) Since Raman scattering efficiency can be enhanced \(10^9 - 10^{14}\) orders of magnitude using plasmonic nanomaterials, researchers have used those materials for developing SERS active diagnosis tools for the identification of infectious virus.\(^ {40-53}\)

Although researchers have made significant advances in this area, nanomaterial-based biodiagnosis is still facing several obstacles. Since nanomaterials often bind nonspecifically with biomolecules, it significantly limits specificity and detection sensitivity.\(^ {34-50}\) In addition, since most of the nanoparticles possess positively or negatively charged surfaces to confer water solubility, they tend to exhibit strong nonspecific binding with protein and other biomolecules in biological fluids.\(^ {20-30,44-50}\) One way to overcome these problems is to design bioconjugated nanomaterial by manipulating biomolecular recognition events (Figure 3A–D).\(^ {20-30,44-50}\) For this...
purpose, we and others used a novel strategy, which is initially coating the nanomaterial with polyethylene glycol (PEG) to reduce charge and nonspecific binding (Figure 3A,B,D). After that, the PEG-coated nanomaterials are conjugated with targeting agents such as the SARS-CoV-2-specific antibody or DNA/RNA/peptide aptamer (Figure 3). Using the above strategy, we have created a bioconjugated nanomaterial-based approach with minimum false alarms and it exhibits high sensitivity and specificity.

The fast-evolving research in this area has led to the development of a bioconjugated zero-dimensional (0D) spherical gold nanoparticle, quantum dots, one-dimensional (1D) carbon nanotubes (CNTs), nanorods, and two-dimensional (2D) graphene, and others for biodiagnosis purposes. All reported nanomaterial-based SARS-CoV-2 diagnosis is based on the nucleic acid- or protein-based detection methodology. In this Account, we present an overview of the recent advances on the use of bioconjugated nanoparticles as an effective diagnosis tool for SARS-CoV-2, which aims to help scientists to understand the use of bioconjugated material for rapid diagnosis and facilitating its early realization of practical clinical applications. To provide the rationale behind these developments, we discuss general mechanisms for different types of bioconjugated nanomaterial-based approaches for the diagnosis of SARS-CoV-2. We also highlight future opportunities and challenges of nanomaterial-based strategies for possible clinical uses.

2. BIOCONJUGATED PLASMONIC NANO PARTICLE FOR TARGETED NAKED EYE DIAGNOSIS

As per WHO, it is vital to expand the COVID-19 testing capacity up to 100-fold over existing RT-PCR tools. For this purpose, easy to use, equipment-free, rapid, and low-cost
colorimetric COVID-19 diagnostic tests can be an excellent choice for point-of-care applications if good sensitivity and specificity can be obtained. Naked eye colorimetric diagnostic tools utilize visual color change to detect targeted analytes.16,21−25 Dye-based colorimetric diagnosis is very well documented in biology from 1884, when Hans Christian Gram developed a naked eye sensor to provide distinct color for Gram-positive and Gram-negative bacteria.20−30,47−54 Since the absorption coefficient for organic dyes is relatively low, the dye-based colorimetric sensor has low sensitivity, and it exhibits poor selectivity.20−30,47−54 To overcome the above problem, researchers have developed a bioconjugated nanomaterial-based colorimetric diagnosis assay, with which selectivity and sensitivity can be enhanced by several orders of magnitude (Figure 4A−D).23−27,47−54 Since for gold nanoparticles, the absorption and scattering occur in the visible region, and it became the golden choice for a colorimetric sensor.23−27,47−54 Due to the very high extinction coefficients (≈10⁸ for 20 nm gold nanoparticle), plasmonic gold nanoparticles absorb light millions of times stronger than the organic dye molecules. As a result, the sensitivity of colorimetric diagnosis tools using gold nanoparticles will be excellent.23−27,47−54 Benefiting from unique localized surface plasmon resonance (LSPR) optical properties, and biocompatible properties, gold nanoparticles are the commonly used plasmonic nanoparticles for the colorimetric diagnosis tools.23−27,47−54 Since its pioneered work by Mirkin and co-workers in 2012,47 researchers have developed a colorimetric assay using the bioconjugated gold nanoparticles (Figure 4A–

**Figure 5.** (A) Scheme showing naked-eye sensing of SARS-CoV-2 RNA using gold nanoparticles capped with antisense oligonucleotides specific for the N-gene. (B) Enhanced dark-field microscope hyperspectral imaging showing antisense oligonucleotide-capped GNP s in the presence of SARS-CoV-2 RNA. Reproduced with permission from ref 16. Copyright 2020 American Chemical Society. (C) Photograph demonstrating the selectivity of the bioconjugated GNP-based colorimetric assay for the COVID-19 antigen. Reproduced with permission from ref 23. Copyright 2021 Royal Society of Chemistry. (D) TEM image of the pseudo-SARS-CoV-2 virus. Reproduced with permission from ref 23. Copyright 2021 Royal Society of Chemistry. (E) Schematic showing the CRISPR/Cas12a system assay with gold nanoparticle-DNA probes for detecting SARS-CoV-2 from clinical samples. (F) Gold nanoparticle-CRISPR/Cas12a system-based detection of SARS-CoV-2 virus, where P represents the virus RNA samples and N represents the blank control. (G) Gold nanoparticle-CRISPR/Cas12a system-based detection of SARS-CoV-2 RNA, where NTC represents no-template control. Reproduced with permission from ref 22. Copyright 2021 American Chemical Society.
### Table 1. Bioconjugated Nanomaterials for the Diagnosis of the SARS-CoV-2 Antigen or Virus

| target molecules | detection platform | bioconjugated nanostructure used | detection time | detection sensitivity | ref |
|------------------|--------------------|---------------------------------|----------------|------------------------|-----|
| SARS-CoV-2 N gene | colorimetric       | RNA/DNA-attached gold nanoparticle | 10 min         | 0.18 ng/μL             | 16  |
| SARS-CoV-2 spike protein | colorimetric | antibody-conjugated gold nanoparticles | 5 min         | 1 ng/mL                | 23  |
| SARS-CoV-2 spike protein | colorimetric | MNAsyme-conjugated gold nanoparticles | 5 min         | 90% for clinical samples | 39  |
| SARS-CoV-2 S, N & P gene | colorimetric       | antibody-conjugated gold nanoparticles | 20 min        | 95% for clinical samples | 21  |
| SARS-CoV-2 IgM/IgG antibodies | colorimetric-based lateral flow | nucleoprotein-attached gold nanoparticles | 15 min        | 93% for clinical samples | 27  |
| SARS-CoV-2 RNA | colorimetric CRISPR/Cas | RNA/DNA-attached gold nanoparticle | 15 min         | 95.2% for clinical samples | 22  |
| SARS-CoV-2 spike protein | SERS | antibody-conjugated gold nanoparticles | 10 min         | 4 pg/mL                 | 23  |
| SARS-CoV-2 spike protein | SERS | antibody-attached graphene | 15 min         | 3.75 fg/mL | 38  |
| SARS-CoV-2 IgM/IgG antibodies | SERS-based LFA | antigen-attached SiO₂@Ag nanoparticle | 20 min        | 100% for clinical samples | 35  |
| SARS-CoV-2 spike protein | SERS | antibody-conjugated gold nanoparticles | 20 min        | 87.7% clinical sample | 42  |
| SARS-CoV-2 spike protein | NSET | aptamer-conjugated gold nanoparticles | 10 min        | 130 fg/mL | 24  |
| SARS-CoV-2 spike protein | fluorescence | ACE2-attached SWCNT | 90 min         | 12.6 nM | 37  |
| SARS-CoV-2 IgG and IgM | fluorescence-based LFA | antigen/SiO₂@Au@QD nanobeads | 15 min        | 100% for clinical samples | 28  |
| SARS-CoV-2 spike protein | NSET | antibody-coated quantum dots | 20 min         | 200 fg/mL | 30  |
| SARS-CoV-2 spike protein | field effect transistor | antibody-coated MXene-grapheene | 50 s           | 1 fg/mL                 | 36  |
| SARS-CoV-2 RNA | RT-PCR | 6 h | 97% for clinical samples | 8    |
| SARS-CoV-2 RNA | CRISPR-Cas | 40 min | 95% for clinical samples | 11   |
| SARS-CoV-2 antigen | LFA | 15 min | 95% for clinical samples | 8    |

C).23,24,45−57 Along these lines, we have reported bioconjugated nanomaterial-based naked eye colorimetric diagnosis of the COVID-19 antigen, SARS-CoV-2 virus, rotavirus, dengue virus, and different superbugs such as Carbapenem-resistant Enterobacteriaceae (CRE) Escherichia coli, Salmonella DT104, and methicillin-resistant Staphylococcus aureus (MRSA).23,24,45,46,52,53

#### 2.1. Fundamentals of Plasmonic Nanoparticle-Based Colorimetric Assays

The colorimetric assay’s working principle is based on LSPR properties of gold nanoparticles, which enables free electrons to oscillate collectively with the direction of the electric field of the incident light.12,16−24,47−57 Due to the presence of LSPR, the boundary of plasmonic gold and silver nanoparticles holds a highly confined and enhanced electromagnetic field, which allows a strong absorption peak in the visible regions.12,16−24,47−50 As a result, plasmonic nanoparticle absorption/extinction or color can be varied by forming aggregates via bioconjugated nanoparticle interactions with analytes.12,16−24,47−50 LSPR coupling among the nanoparticles can be manipulated by changing the distance between gold nanoparticles or by varying the degree of aggregation of nanoparticles (Figure 4D−G).24,47−57 To understand better about the distance dependence of the LSPR coupling mechanism, our group reported experimental and theoretical investigation by separating nanoparticles by double-strand DNA (Figure 4E−G).31 Theoretically, finite difference time domain (FDTD) simulation investigation indicates that the plasmon coupling is highly dependent on the distance between two nanoparticles (Figure 4G).31

#### 2.2. Targeted Naked Eye Colorimetric Diagnosis of the SARS-CoV-2 RNA, Antigen, and Virus

Inspired by the color variations after aggregations, researchers have designed the fast-developing field of naked eye colorimetric nanosensors to diagnose the SARS-CoV-2 RNA, the antigen, and the virus itself (Figure 5A−G).16,21−25 In an exciting strategy, the thiol-modified antisense oligonucleotides functionalized gold nanoparticle has been used for colorimetric detection of the N gene (nucleocapsid phosphoprotein) of SARS-CoV-2 (Figure 5A,B).16 Bioconjugated gold nanoparticles agglomerate selectively in the presence of RNA sequence of SARS-CoV-2 (Figure 5A),16 which can be diagnosed within 10 min.

The selectivity of the assay has been demonstrated using MERS-CoV viral RNA16. The reported detection limit was 0.18 ng/μL for targeted RNA (Table 1).16 Motivated by the simplicity of the assay, we have developed an antispike antibody-attached GNP-based colorimetric assay for rapid COVID-19 antigen diagnosis.23 In the presence of the SARS-CoV-2 spike recombinant antigen, due to the antigen–antibody interaction, a colorimetric change from purple to bluish color is observed with the naked eye (Figure 5D). The SARS-CoV-2 antigen can be diagnosed within 10 min, and the detection limit for the colorimetric assay was obtained to be 1 ng/mL (Table 1).23 Furthermore, the selectivity for naked eye assay has been demonstrated using the severe acute respiratory syndrome coronaviruses (SARS-CoV) nucleoprotein antigen and the Middle East respiratory syndrome coronavirus (MERS-CoV) nucleoprotein antigen separately (Figure 5D).23 The sensitivity of the colorimetric assay for the identification of coronavirus was obtained as 1000 virus particles/mL.23

The CRISPR system has been known since 1987, just five years before CRISPR-based diagnoses became popular for human pathogen diagnosis.11,15,18−22 Recently scientists have developed CRISPR/Cas12a and CRISPR/Cas13a, systems for the designing rapid and sensitive detection of SARS-CoV-2.11,15,18−22 To improve the sensitivity of CRISPR detection, the SPR properties of plasmonic gold nanoparticles have been used to pair with the CRISPR-Cas12a system (Figure 5E).22 Reported data indicate that CRISPR/Cas12a-assisted detection using a gold nanoparticle as the colorimetric probe has the capability to distinguish the N gene and O gene of SARS-CoV-2 from two other closely related coronaviruses (Figure 5F,G).22 Experimental data show that that the gold nanoparticle-CRISPR-Cas12a system can be used to detect as low as 50 RNA copies.22 From the reported data, we can conclude that the gold nanoparticle-CRISPR-Cas12a system has...
potential for SARS-CoV-2 screening in clinics where state-of-the-art facilities are lacking.

2.3. Naked Eye Diagnosis of SARS-CoV-2 from Clinical Sample

Using similar strategies, the antibody-conjugated gold nanoparticle-based colorimetric assay has been used for SARS-CoV-2 identification in clinical samples from 45 positive to SARS-CoV-2 patients and 49 negative patients. For this purpose, gold nanoparticles were attached with three surface proteins of SARS-CoV-2 (spike, envelope, and membrane) (Figure 6A,B). The reported sensitivity and specificity of the colorimetric assay were higher than 95% (Table 1). For clinical samples, the GNP-based colorimetric essay can be compared with a real-time PCR. The viral load’s corresponding threshold cycle (Ct) = 36.5 can be detected using gold nanoparticle-based colorimetric assay.21

Similarly, recently researchers have used the gold nanoparticle–CRISPR/Cas12a system to analyze clinical SARS-CoV-2 RNA (Figure 6C,D). Reported data show 95.12% consistency with clinically approved PCR data, which indicates that gold nanoparticle–CRISPR/Cas12a has potential for SARS-CoV-2 screening in clinics.

Due to the enormous advantages of portability, the lateral flow assay (LFA) using bioconjugated gold nanoparticles has been developed. It is now well documented that
antibodies against SARS-CoV-2 will be produced by the human body after infection, which is the primary immune response to fight against COVID-19.27-32 To design a possible point of care device for SARS-CoV-2, gold nanoparticle-based lateral-flow strips have been developed for rapid identification of the IgM antibody against the SARS-CoV-2 virus (Figure 5G).27 Reported positive and negative SARS-CoV-2 serum sample data demonstrate a good consistency with RT-PCR data, and the specificity is 93.3% (Figure 5G).27 It should be noted that since it takes 7-14 days to produce antibodies after an infection, gold nanoparticle-based LFA cannot be used for early detection. All reported clinical sample data discussed here indicate that a bioconjugated nanomaterial-based naked eye assay can be used for the design of inexpensive platforms for virus diagnosis on a mass scale for countries where health systems are lacking state-of-the-art laboratory infrastructure.

Although bioconjugated GNP-based colorimetric assay is very rapid and requires minimal equipment, due to the low sensitivity, use of the assay for an early stage of the SARS-CoV-2 infection is limited. To overcome the above problem, researchers are working to develop nanomaterial-based ultra-sensitive tools for SARS-CoV-2.

3. BIOCONJUGATED GRAPHENE AND PLASMONIC NANOMATERIAL-BASED SERS FOR HIGHLY SENSITIVE DIAGNOSIS OF CORONAVIRUS

A paradigmatic example of the highly sensitive diagnostic method is nanomaterial-based surface-enhanced Raman scattering (SERS) spectroscopy, as it has the capability for very low-level specific identification of virus, bacteria, and fingerprint identification of pathogens.23,24,45,46,51-54 After the discovery of SERS in 1974, it is known to be one of the most sensitive detection techniques for biomolecular sensing (Figure 7A-F).51-54 It is well understood that placing the analyte within nanometer-sized gaps between two plasmonic nanoparticles is very important to enable massive enhancement of the Raman signals.23,24,45,46,51-54 (Figure 7B). Along these lines, we have reported bioconjugated nanomaterial-based SERS for the
diagnosis of the COVID-19 antigen, SARS-CoV-2 virus, rotavirus, dengue virus, West Nile virus, different superbugs, and cancer biomarkers.\textsuperscript{23,24,45,46,53}

3.1. Fundamentals of Nanomaterial-Based SERS Assays

SERS enhancement is based on electromagnetic as well as chemical enhancement mechanisms.\textsuperscript{51–53} SERS exploits the strong electromagnetic fields generated at the interparticle junctions of plasmonic nanostructures, known as "plasmonic hot spots" (Figure 7B, C).\textsuperscript{51–54} The strong plasmon coupling in the "hot spots" allows Raman signals to be enhanced by 10\textsuperscript{8}–10\textsuperscript{10} orders of magnitude, which is sufficient to detect analytes at single molecular level.\textsuperscript{51–54} Since SERS electromagnetic enhancement factor is proportional to the fourth power of the plasmonic enhancement electric field (\([E]^4\)), FDTD simulation data indicate that the enhancement factor can be 6–8 orders magnitude higher in the "hot spot" position (Figure 7B).\textsuperscript{51–54} Similarly, SERS chemical enhancement depends on the charge transfer between analytes and nanostructures.\textsuperscript{51–54}

3.2. Targeted SERS Diagnosis of the SARS-CoV-2 Antigen and Virus

Due to the excellent sensitivity and potable sensor development capability, we have developed a SERS assay for COVID-19 antigen and virus identification using bioconjugated gold nanoparticles (Table 1 and 2 and Figures 7 and 8).\textsuperscript{23} For this purpose, 4-aminothiophenol (4-ATP) SERS reporter and antispoke antibody-attached GNP have been developed.\textsuperscript{23} Due to the strong interaction via plasmon-excitation coupling, the SERS assay has the capability to diagnose 1 pg/mL antigen (Figure 7D and Table 1).\textsuperscript{23} Selectivity for the SERS assay has been demonstrated using the severe acute respiratory syndrome coronaviruses (SARS-CoV) nucleoprotein antigen and the Middle East respiratory syndrome coronavirus (MERS-CoV) nucleoprotein antigen separately (Figure 7D).\textsuperscript{23}

In an interesting study, recently, antibody-attached graphene has been used as a Raman transducer for the detection of COVID-19 S-protein (Figure 7E,F).\textsuperscript{35} Reported data show no measurable cross-reactivity with the MERS-CoV spike protein.\textsuperscript{35} Experimental data demonstrate that antibody-attached graphene-based Raman has the capability to detect SARS-CoV-2 spike protein as low as the 3.75 fg/mL level in saliva\textsuperscript{38} (Table 1). Although Raman reporter-based SERS has very high sensitivity, the sensing assay will have huge benefits if the diagnostic technologies can be used as fingerprinting identification.\textsuperscript{51–54} In the last few decades, researchers have developed several sensing technologies to target the above goal.\textsuperscript{51–54} Among them, label-free SERS has attracted considerable attention, which has the capability for unique fingerprint profiling of a biological sample.\textsuperscript{51–54}

Taking the above advantage of Raman spectroscopy-based assay, we have demonstrated that antibody-attached GNP-based SERS has the capability to be used for fingerprint identification of dengue, West Nile, rotavirus, and coronavirus, respectively (Figure 8A–D, Table 2).\textsuperscript{23,45,46} Raman bands from pseudo-SARS-CoV-2 can be assigned to spike protein phenylalanine ring breath mode, amide II, and amide III modes (Table 2 and Figure 8C). Raman modes due to lipid and unsaturated lipids are also powerful (Table 2 and Figure 8C). From all the spectra, one can find that the Raman bands for lipid and phospholipids are unique for coronavirus spike protein which has not been observed for dengue, West Nile, or rotavirus\textsuperscript{23,45,46} (Table 2 and Figure 8).

3.3. SERS-Based Diagnosis of the SARS-CoV-2 Antigen and Antibody from a Clinical Sample

Similarly, the gold nanoparticle-based SERS assay has been used for the SARS-CoV-2 spike antigen identification in a clinical sample using throat swabs from 102 healthy people and 30 confirmed COVID-19 patients (Figure 9A–H).\textsuperscript{42} For this purpose, deep learning-based SERS has been developed for on-site detection of the SARS-CoV-2 antigen, using human throat swabs and sputum samples (Figure 9A–C).\textsuperscript{42} Raman bands show that SERS can be used for SARS-CoV-2 antigen detection within 2 min time period with an accuracy of 87.7% from clinical sample.\textsuperscript{42}

Since LFA is the paper-based cheapest tool for achieving rapid screening, the researcher has developed SERS-based LFA for SARS-CoV-2 IgM/IgG detection. For this purpose, SERS tags were fabricated by coating a complete Ag shell on the SiO\textsubscript{2} core.\textsuperscript{55} The reported result indicates that SERS-LFA strips have the capability to detect SARS-CoV-2 IgM/IgG within 25 min from the clinical sample with 100% accuracy.\textsuperscript{55} All the clinical sample data discussed here indicate that bioconjugated graphene and GNP nanomaterial-based SERS have the capability to be used for the diagnosis of SARS-CoV-2 in-clinics.

Since genetic variants of SARS-CoV-2 such as B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma) are circulating, whose infection rates are much higher than the original version first detected in China, we anticipate that researchers will design many more innovative strategies in the coming years for the fingerprint Raman sensing of different variants.

4. CNT AND FLUORESCENCE NANOPARTICLE-BASED SENSOR FOR SARS-COV-2 SENSING

In the last two centuries, light microscopy became the most used technique in clinical diagnosis.\textsuperscript{57} Last decade, we and others demonstrated that carbon dots (CDs), perovskite quantum dots (PQDs), semiconductor quantum dots, and lanthanum nanoparticles have been proven to be better fluorescent probes than conventional fluorescent dyes.\textsuperscript{57}
Since fluorescence nanodots exhibit a much higher quantum yield than organic dyes and nanodots and are resistant to photobleaching, researchers have used them in a variety of biodetection and imaging purpose.\textsuperscript{55–57}

4.1. CNT-Based Fluorescence Sensor for SARS-CoV-2 Sensing

In an exciting study recently, single-walled carbon nanotubes (SWCNTs), which emit near-infrared emission, have been used to develop a nanosensor for the detection of SARS-CoV-2 (Figure 10A–D).\textsuperscript{37} For this purpose, SWCNTs were noncovalently functionalized with angiotensin-converting enzyme 2 (ACE2), which has a very high binding affinity for a spike protein (Figure 10A).\textsuperscript{37}

Since CNT exhibits near-infrared (NIR) emission in a biological II window, it has been used as signal transducers for spike protein detection (Figure 10B). Reported data indicate that when viral S proteins are present, the fluorescence signal from SWCNT changes due to the binding between ACE2 and spike protein (Figure 10B–D).\textsuperscript{37} Reported data demonstrate that bioconjugated SWCNT can be used for the identification of SARS-CoV-2 virus-like particles within 5 s of exposure time.\textsuperscript{37} The detection limit was reported as 12.6 nM. (Table 1). Continuing innovations on the design of smart nanomaterial-based robust fluorescence assay will undoubtedly further expedite the development to achieve clinical testing performance.

4.2. Fundamentals of Nanomaterial-Based FRET Assays

Although researchers have made huge advances in the design of the fluorescence microscope, it is now well documented that the fluorescence microscope resolution is not enough for understanding the interaction between biomolecules.\textsuperscript{24,55–57} To overcome the above problem, researchers have developed a Förster or Fluorescence Resonance Energy Transfer (FRET) microscope that has the capability to determine the spatial proximity of biomolecules.\textsuperscript{55–57}

FRET was discovered by Theodor Förster in 1948, where the excited donor transfers energy to the ground state acceptor, which has been used routinely as a biosensor in the scientific community.\textsuperscript{24,55–57} In the last three decades, due to the advancement in state-of-the-art digital imaging techniques, FRET-based light microscopy imaging has become very popular. It has been used to monitor the dynamics of biomolecules in vitro and in vivo.\textsuperscript{24,55–57} FRET has been used in biological research routinely due to the dipole–dipole coupling mechanism between a donor and an acceptor, and the maximum distance limit for biomolecular interaction measurement is 10 nm for FRET.\textsuperscript{24,55–57} To overcome this 10 nm distance limit, we and other groups have reported a long-range nanoparticle-based surface energy transfer (NSET), where energy transfer can be monitored even above 20 nm distance (Figure 11A,B).\textsuperscript{24,55–57} Since the quenching efficiency of the gold nanoparticle is 9–10 orders of magnitude higher than that of the organic acceptor used for FRET, the GNP-based NSET nanoprobe has a much higher efficiency than FRET.\textsuperscript{24,55–57}

4.3. Targeted FRET Diagnosis of the SARS-CoV-2 Antigen and Virus

Using the above advantages of NSET and aptamer-based biorecognition technology, we have developed rhodamine 6G (Rh-6G) dye-conjugated COVID-19 spike protein-specific DNA aptamer-attached gold nanostar-based NSET, which can be used for rapid diagnosis of the COVID-19 antigen or virus (Figure 11D–F).\textsuperscript{24} Due to the strong interaction between aptamers and the COVID-19 spike antigen via noncovalent interaction, the...
reported NSET assay has the capability to diagnose 130 fg/mL antigen (Table 1, Figure 11D–F).

Similarly, using the DNA aptamer–spike protein interaction, NSET has been used for the identification of virus with the sensitivity of 8 virus particles/mL (Table 1).

For the possible application of the NSET assay for COVID-19 from clinical sample, the NSET assay has been used to detect antigen and virus in the infected nasal matrix. Interestingly, the NSET has the capability to be used for the detection of the COVID-19-specific antigen at a concentration of 100 fg/mL and virus at the concentration of 20 virus particles/mL (Figure 11F).

Using similar strategies, a FRET sensor based on the fluorescent QDs (green QD514, fluorescence maximum at 514 nm) and gold nanoparticles have been developed to monitor in vitro spike-ACE2 binding (Figure 12A,B). Experimentally reported data indicate that QD fluorescence is quenched upon binding due to the change in distance between gold nanoparticles and QDs (Figure 12A,B). Reported data demonstrate that FRET intensity could be disrupted by unlabeled ACE2 or by neutralizing SARS-CoV-2 antibodies (Figure 12A,B). The in vitro data indicate that FRET platform can be used for rapid screening of SARS-CoV-2 infection.

4.4. FRET-Based Diagnosis of SARS-CoV-2 Antibody from Clinical Samples

Since fluorescence-based LFA can be an easy-to-use point of care device for society, the researchers have developed a high-sensitivity, portable fluorescence lateral flow test strip for early detection of IgM and IgG in human serum (Figure 12C).

For this purpose, aggregation-induced emission (AIE) dye-loaded nanoparticle-based LFA was designed (Figure 12C). Using 172 COVID samples from clinics, the reported data show that the sensitivities of AIE810NP-based test strips are 78 and 95% in detecting IgM and IgG, respectively. Fluorescence-based LFA data are comparable with the ELISA data, which show...
that the sensitivities are 85 and 95% for IgM and IgG, respectively.19

Reported clinical sample data indicate that bioconjugated nanomaterial-based NSET may pave new roads for SARS-CoV-2 detection in clinics. Although reported data are exciting, in the future, researchers need to design robust, reusable, and cheap substrates, so that it can be applied in inadequate clinical laboratories.

5. CONCLUSIONS AND OUTLOOK

In this Account, we introduced how bioconjugated nanomaterials have been used in the last few months for possible applications in SARS-CoV-2 diagnostics. We summarized recent efforts to harness the diversity of structures, surface chemistry, and plasmonic properties of nanomaterials for the development of naked-eye colorimetric identification of the SERS-CoV-2 viral RNA, antigen, and antibody. The reported clinical sample shows that a bioconjugated nanomaterial-based naked eye assay can be used for the design of inexpensive platforms for virus diagnosis, which is critical for low- and middle-income countries. We have also discussed how bioconjugated nanomaterial-based, highly sensitive SERS and NSET assays have been designed for the identification of the SARS-CoV-2 virus, antigen, and antibody from a clinical sample. As material design for the diagnosis of SARS-CoV-2 is still in its infancy, which started less than two years before, the works presented here are the initial steps toward the new development. Since clear proof of concept exists, after continuing innovations on proper engineering design, the device will achieve clinical testing performance for rapid, accurate, and massive infection diagnosis. One smart way to

Figure 10. (A) Scheme showing the ACE2-SWCNT nanosensor working principle. (B) Spectra showing how the fluorescence spectrum of ACE2-SWCNT varies with time. (C) Plot showing the selectivity of the sensor for the SARS-CoV-2 spike receptor-binding domain (S RBD) and SARS-CoV-1 S RBD with respect to MERS S RBD and FLU hemagglutinin subunit (HA1). (D) ACE2-SWCNT nanosensor response after exposure to 1 μM S RBD in the presence of 1% viral transport medium (VTM), saliva, nasal fluid, and sputum (treated with sputasol). Reproduced with permission from ref 37. Copyright 2021 American Chemical Society.

Figure 11. (A) Schematic representation of the NSET ruler with difference lengths. (B) Variation of quenching efficiency with separation distance for the NSET ruler. Reproduced with permission from ref 47. Copyright 2012 American Chemical Society. (C) Schematic indicating the design of the NSET assay using a gold nanostar and a COVID-specific aptamer. (D) Variation of NSET intensity with the concentration of pseudo-SARS-CoV-2 virus. (E) Single-photon luminescence image of pseudo-baculovirus-attached dye-conjugated aptamer. Reproduced with permission from ref 24. Copyright 2021 American Chemical Society.
design such a device is by combining nanomaterial-based devices with CRISPR recognition, which has the capability for unprecedented detection performance.

Despite the considerable achievements made in the last year on the design of bioconjugated nanomaterial, the major fundamental challenge is the development of cost-effective, biocompatible, and environmentally friendly nanomaterials, which have the capability to exhibit high selectivity, sensitivity, accuracy, and precision for real-life infectious disease marker sensing applications. With time it is now clear that slowly COVID-19 is becoming an endemic disease. As a result, researchers need to find out multifunctional material-based devices, which have the capability to test and to differentiate between different coronavirus variants.

To further promote this field to help survival in the current and future pandemics, the researchers need to explore the design of mass-producible synthetic process for biofunctionalized nanomaterials, where size, shape, defects, and stability can be controlled. Future theoretical and experimental efforts are necessary for profound understanding on how to control the batch-to-batch design process, so that it will have higher potential for healthcare applications. Ultimately, the performance of the sensor in clinics will vary if the shelf life of bioconjugated substrates is short and minimization of nonspecific binding cannot be controlled in clinics. Further exploration on the design of a robust and stable immobilization technique is highly desired. For achieving best positive outcomes, a collaborative effort with the clinical sector to receive their feedback on the novel bioconjugated material-based sensor performance is very important for improving the accuracy of the diagnostic device and design of no or minimum toxic novel materials for the health care industry. As history taught us that crisis could create new potential for discovery, the current pandemic could inspire all scientists to reshape the future of the material field for complex biological systems.

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REFERENCES
(1) Morens, D. M.; Folksers, G. K.; Fauci, A. S. Emerging infections: a perpetual challenge. Lancet Infect Dis 2008, 8, 710−719.
(2) Huremovic, D. Brief History of Pandemics (Pandemics Throughout History). Psychiatry Pandemics 2019, 7, 3−35.
(3) Jones, D. S. History in a Crisis—Lessons for Covid-19. N. Engl. J. Med. 2020, 382, 1681−1683.
(4) Wang, C.; Horby, P. W.; Hayden, F. G.; Gao, G. F. A novel coronavirus outbreak of global health concern. Lancet 2020, 395, 470−473.
(5) Gates, B. Responding to Covid-19—A Once-in-a-Century Pandemic? N. Engl. J. Med. 2020, 382, 1677−1679.
(6) Phillips, N. The Coronavirus Will Become Endemic. Nature 2021, 590, 382−384.
(7) Vandenberg, O.; Martiny, D.; Rochas, O.; van Belkum, A.; Kozlakidis, Z. Considerations for Diagnostic COVID-19 Tests. Nat. Rev. Microbiol. 2021, 19, 171−183.
(8) Valera, E.; Jankelow, A.; Lim, J.; Kindratenko, V.; Ganguli, A.; White, K.; Kumar, J.; Bashir, R. COVID-19 Point-of-Care Diagnostics: Present and Future. ACS Nano 2021, 15 (5), 7899−7906.
(9) Derakhshan, M. A.; Amani, A.; Faridi-Majidi, R. State-of-the-Art of Nanodiagnostics and Nanotherapeutics against SARS-CoV-2. ACS Appl. Mater. Interfaces 2021, 13 (13), 14816−14843.
(10) Zhang, L.; Lin, D.; Sun, X.; Curth, U.; Drosten, C.; Sauerlending, L.; Becker, S.; Rox, K.; Hilgenfeld, R. Crystal Structure of SARS-CoV-2 Main Protease Provides a Basis for Design of Improved α-Ketoamide Inhibitors. Science 2020, 368, 409−412.
(11) Yue, H.; Huang, M.; Tian, T.; Xiong, E.; Zhou, X. Advances in Clustered, Regularly Interspaced Short Palindromic Repeats (CRISPR)-Based Diagnostic Assays Assisted by Micro-/Nano-technologies. ACS Nano 2021, 15 (5), 7848−7859.
(12) Tang, Z.; Kong, N.; Zhang, X.; Liu, Y.; Hu, P.; Mou, S.; Liljestrom, P.; Shi, J.; Tan, W.; Kim, J. S.; Cao, Y.; Langer, R.; Leong, K. W.; Farokhzad, O. C.; Tao, W. A Materials-Science Perspective on Tackling COVID-19. Nat. Rev. Mater. 2020, 5, 847−860.
(13) Wang, C.; Li, W.; Drabek, D.; Okba, N. M. A.; van Haperen, R.; Osterhaus, A. D. M. E.; van Kuppevelt, F. J. M.; Haagmans, B. L.; Grosfeld, V.; Bosch, B. J. A Human monoclonal antibody blocking SARS-CoV-2 infection. Nat. Commun. 2020, 11 (1), 2251.
(14) Huang, H.; Yang, L.; Fan, C. H.; Li, M.; Nie, H. L.; Wang, F. B.; Wang, H.; Wang, R.; Xia, J. B.; Zheng, X.; Zuo, X. L.; Huang, J. X. Covid-19: A Call for Physical Scientists and Engineers. ACS Nano 2020, 14, 3747−3754.
(15) Ding, X.; Yin, K.; Li, Z.; Lalla, R. V.; Ballesteros, E.; Sfeir, M. M.; Liu, C. Ultra-sensitive and Visual Detection of SARS-CoV-2 Using All-in-One Dual CRISPR-Cas12a Assay. Nat. Commun. 2020, 11, 4711.
(16) Moitra, P.; Alafeef, M.; Dighe, K.; Frieman, M. B.; Pan, D. Selective Naked-Eye Detection of SARS-CoV-2 Mediated by N Gene Targeted Antisense Oligonucleotide Capped Plasmonic Nanoparticles. ACS Nano 2020, 14, 7617−7627.
(17) Seo, G.; Lee, G.; Kim, M. J.; Baek, S. H.; Choi, M.; Ku, K. B.; Lee, C. S.; Jun, S.; Park, D.; Kim, S. J.; Lee, J. O.; Kim, B. T.; Park, E. C.; Kim, S. Rapid Detection of COVID-19 Caustive Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor-Based Biosensor. ACS Nano 2020, 14, 5135−5142.
(18) Choi, J.; Lim, J.; Shin, M.; Paek, S.; Choi, J. CRISPR-Cas12a-Based Nucleic Acid Amplification-Free DNA Biosensor via Au Nanoparticle-Assisted Metal-Enhanced Fluorescence and Colorimetric Analysis. Nano Lett. 2021, 21, 693−699.
(19) Chen, R.; Ren, C.; Liu, M.; Ge, X.; Qu, M.; Zhou, X.; Liang, M.; Lu, Y.; Li, F. Early Detection of SARS-CoV-2 Serum conversion in Humans with Aggregation-Induced Near-Infrared Emission Nanoparticle-Labeled Lateral Flow Immunassay. ACS Nano 2021, 15, 8996−9004.
(20) Yadav, S.; Sadique, M. A.; Ranjan, P.; Kumar, N.; Singhal, A.; Srivastava, A. K.; Khan, R. SERS Based Lateral Flow Immunassay for Point-of-Care Detection of SARS-CoV-2 in Clinical Samples. ACS Applied Bio Materials 2021, 4 (4), 2974−2985.
(21) Ventura, B. D.; Cennamo, M.; Minopoli, A.; Campanile, R.; Censi, S. B.; Terraciano, D.; Portella, G.; Velotta, R. Colorimetric Test for Fast Detection of SARS-CoV-2 in Nasal and Throat Swabs. ACS sensors 2020, 5, 3043−3048.
(22) Jiang, Y.; Hu, M.; Liu, A. N.; Lin, Y.; Liu, L.; Yu, B.; Zhou, X.; Pan, D. W. Detection of SARS-CoV-2 by CRISPR/Cas12a-Enhanced Colorimetry. ACS Sens. 2021, 6 (3), 1086−1093.
(23) Pramanik, A.; Gao, Y.; Patibandla, S.; Mitra, D.; McCandless, M. G.; Fassero, L. A.; Gates, K.; Tandon, R.; Ray, P. C. Rapid Diagnosis and Effective Inhibition of Corona Virus Using Spike Antibody Attached Gold nanoparticle. Nanoscale Advances 2021, 3, 1588−1596.
(24) Pramanik, A.; Gao, Y.; Patibandla, S.; Mitra, D.; McCandless, M. G.; Fassero, L. A.; Gates, K.; Tandon, R.; Ray, P. C. Aptamer Conjugated Gold Nanostar-Based Distance-Dependent Nanoparticle Surface Energy Transfer Spectroscopy for Ultrasensitive Detection and Inactivation of Corona Virus. J. Phys. Chem. Lett. 2021, 12, 2166−2171.
(25) Alafeef, M.; Dighe, K.; Moitra, K.; Pan, D. Rapid, Ultrasensitive, and Quantitative Detection of SARS-CoV-2 Using Antisense Oligonucleotides Directed Electrochemical Biosensor Chip. ACS Nano 2020, 14, 17028−17045.
(26) Zhang, Z.; Tang, Z.; Farokhzad, N.; Chen, T.; Tao, W. Sensitive, Rapid, Low-cost and Multiplexed COVID-19 Monitoring by the Wireless Telemedicine Platform. Matter 2020, 3, 1818−1820.
(27) Huang, C.; Wen, T.; Shi, F.; J.; Zeng, X.-Y.; Jiao, Y.-J. Rapid Detection of IgM Antibodies against the SARS-CoV-2 Virus via
Colloidal Gold Nanoparticle-Based Lateral-Flow Assay. ACS Omega 2020, 5, 12550.

(28) Wang, C.; Yang, X.; Gu, B.; Liu, H.; Zhou, Z.; Shi, L.; Cheng, X.; Wang, S. Sensitive and Simultaneous Detection of Sars-Cov-2-Specific IgM/IgG Using Lateral Flow Immunassay Based on Dual-Mode Quantum Dot Nanobeads. Anal. Chem. 2020, 92 (23), 15542−15549.

(29) Wang, Z.; Zheng, Z.; Hu, H.; Zhou, Q.; Liu, W.; Li, X.; Liu, Z.; Wang, Y.; Ma, Y. A Point-of-Care Selenium Nanoparticle-Based Test for the Combined Detection of Anti-Sars-Cov-2 IgM and IgG in Human Serum and Blood. Lab Chip 2020, 20 (22), 4255−4261.

(30) Gorschkov, K.; Susumu, K.; Chen, J.; Xu, M.; Pradhan, M.; Zhu, W.; Hu, X.; Breger, J. C.; Wolak, M.; Oh, E. Quantum Dot-Conjugated Sars-Cov-2 Spike Pseudo-Virions Enable Tracking of Angiotensin Converting Enzyme 2 Binding and Endocytosis. ACS Nano 2020, 14 (9), 12234−12247.

(31) Chen, Z.; Zhang, Z.; Zhai, X.; Li, Y.; Lin, L.; Zhao, H.; Bian, L.; Li, P.; Yu, L.; Wu, Y.; Lin, G. Rapid and Sensitive Detection of Anti-Sars-Cov-2 IgM Using Lanthanide-Doped Nanoparticles-Based Lateral Flow Immunassay. Anal. Chem. 2020, 92 (10), 7226−7231.

(32) Xiong, H.; Ye, X.; Li, Y.; Qi, J.; Fang, X.; Kong, J. Efficient Microfluidic-Based Air Sampling/Monitoring Platform for Detection of Aerosol SARS-CoV-2 On-site. Anal. Chem. 2021, 93, 4270−4276.

(33) Hristov, D.; Rijal, H.; Gomez-Marquez, J.; Hamad-Schifferli, K. Developing a Paper-Based Antigen Assay to Differentiate between Coronavirus and SARS-CoV-2 Spike Variants. Anal. Chem. 2021, 93, 7825−7832.

(34) Yao, Z.; Zhang, Q.; Zhu, W.; Galluzzi, M.; Zhou, W.; Li, J.; Zayats, A. V.; Yu, X. F. Rapid detection of SARS-CoV-2 viral nucleic acids based on surface enhanced infrared absorption spectroscopy. Nanoscale 2021, 13, 10133−10142.

(35) Liu, H. F.; Dai, E. H.; Xiao, R.; Zhou, Z. H.; Zhang, M. L.; Bai, Z. K.; Shao, Y.; Qi, K. Z.; Tu, J.; Wang, C. W.; Wang, S. Q. Development of a SERS-Based Lateral Flow Immunassay for Rapid and Ultra-Sensitive Detection of Anti-SARS-CoV-2 IgM/IgG in Clinical Samples. Sens. Actuators, B 2021, 329, 129196.

(36) Li, Y.; Peng, Z.; Holl, N. J.; Hassan, M. F.; Pappas, J. M.; Wei, C.; Izadi, O. H.; Wang, Y.; Dong, X.; Wang, C.; Huang, Y. W.; Kim, D. Y.; Wu, C. MXene—Graphene Field-Effect Transistor Sensing of Influenza Virus and SARS-CoV-2. ACS Omega 2021, 6 (10), 6643−6653.

(37) Pinals, R. L.; Ledesma, F.; Yang, D.; Navarro, N.; Jeong, S.; Pak, J. E.; Kuo, L.; Chuang, Y. C.; Cheng, Y. W.; Sun, H. Y.; Landry, M. P. Rapid SARS-CoV-2 Spike Protein Detection by Carbon Nanotube-Based Near-Infrared Nanosensors. Nano Lett. 2021, 21, 2272−2280.

(38) Nguyen, N. H. L.; Kim, S.; Lindemann, G.; Berry, V. COVID-19 Spike Protein Induced Phononic Modification in Antibody-Coupled Graphene for Viral Detection Application. ACS Nano 2021, 15 (7), 11743−11752.

(39) Liu, Y.; Wang, J.; Xiong, Q.; Hornburg, D.; Tao, W.; Farokhzad, O. C. Nano-Bio Interactions in Cancer: From Therapeutics Delivery to Early Detection. Acc. Chem. Res. 2021, 54, 291−301.

(40) Chen, H.; Park, S. G.; Choi, N.; Kwon, H. J.; Kang, T.; Lee, M. K.; Choo, J. Sensitive Detection of SARS-CoV-2 Using a SERS-Based Aptasensor. ACS Sens. 2021, 6, 2378−2385.

(41) Calomagno, C.; Bertazzi, D.; Gualeri, A.; Picciolini, S.; Banfi, P. I.; Lax, A.; Messina, E.; Navarro, J.; Bianchi, L.; Caronni, A.; Marenco, F.; Monteleone, S.; Arienti, C.; Bedoni, M. COVID-19 salivary Raman fingerprint: innovative approach for the detection of current and past SARS-CoV-2 infections. Scientific Report 2021, 11, 4943.

(42) Huang, J.; Wen, J.; Zhou, M.; Ni, S.; Le, W.; Chen, G.; Wei, L.; Zeng, Y.; Qi, D.; Pan, M.; et al. On-Site Detection of SARS-CoV-2 Antigen by Deep Learning-Based Surface-Enhanced Raman Spectroscopy and Its Biochemical Foundations. Anal. Chem. 2021, 93, 9174−9182.

(43) Song, Y.; Song, J.; Wei, X.; Huang, M.; Sun, M.; Zhu, L.; Lin, B.; Shen, H.; Zhu, Z.; Yang, C. Discovery of Aptamers Targeting the Receptor-Binding Domain of the SARS-CoV-2 Spike Glycoprotein. Anal. Chem. 2020, 92, 9895−9900.

(44) Viraka Nellore, B. P.; Kanchanapally, R.; Pramanik, A.; Sinha, S. S.; Chavva, S. R.; Hamme, A.; Ray, P. C. Aptamer-Conjugated Graphene Oxide Membranes for Highly Efficient Capture and Accurate Identification of Multiple Types of Circulating Tumor Cells. Bioconjugate Chem. 2015, 26, 235−242.

(45) Paul, A. M.; Fan, Z.; Sinha, S. S.; Shi, Y.; Le, L.; Bai, F.; Ray, P. C. Bioconjugated Gold Nanoparticle Based SERS Probe for Ultrasensitive Identification of Mosquito-Borne Viruses Using Raman Fingerprinting. J. Phys. Chem. C 2015, 119, 23669−23675.

(46) Fan, Z.; Yust, B.; Nellore, B. P. V.; Sinha, S. S.; Kanchanapally, R.; Crouch, R. A.; Pramanik, A.; Chavva, S. R.; Sardar, D.; Ray, P. C. Accurate Identification and Selective Removal of Rotavirus Using a Plasmonic-Magnetic 3D Graphene Oxide Architecture. J. Phys. Chem. Lett. 2014, 5, 3216−3221.

(47) Cutler, J. I.; Auyeung, E.; Mirkin, C. A. Spherical nucleic acids. J. Am. Chem. Soc. 2012, 134 (3), 1376−91.

(48) Rosi, N. L.; Mirkin, C. A. Nanostructures in Biodiagnostics. Chem. Rev. 2005, 105, 1547−1562.

(49) Farokhzad, N.; Tao, W. Materials chemistry-enabled platforms in detecting sexually transmitted infections: progress towards point-of-care tests. Trends in Chemistry 2021, 3, 589−602.

(50) Mu, Q.; Jiang, G.; Chen, L.; Zhou, H.; Fourches, D.; Tropsha, A.; Yan, B. Chemical Basis of Interactions between Engineered Nanoparticles and Biological Systems. Chem. Rev. 2014, 114, 7740−7781.

(51) Sinha, S. S.; Paul, D. K.; Kanchanapally, R.; Pramanik, A.; Chavva, S. R.; Viraka Nellore, B. P.; Jones, J. S.; Ray, P. C. Long-range Two-photon Scattering Spectroscopy Ruler for Screening Prostate Cancer Cells. Chem. Sci. 2015, 6, 2411−2418.

(52) Sinha, S. S.; Jones, S.; Pramanik, A.; Ray, P. C. Nanoarchitecture Based SERS for Biomolecular Fingerprinting and Label-Free DiseaseMarkers Diagnosis. Acc. Chem. Res. 2016, 49, 2725−2735.

(53) Jones, S.; Sinha, S. S.; Pramanik, A.; Ray, P. C. Three-dimensional (3D) plasmonic hot spots for label-free sensing and effective photothermal killing of multiple drug resistant-superbugs. Nanoscale 2016, 8, 18301−18308.

(54) Singh, A. K.; Khan, S. A.; Fan, Z.; Demeritte, T.; Senapati, D.; Kanchanapally, R.; Ray, P. C. Development of a Long-Range Surface-Enhanced Raman Spectroscopy Ruler. J. Am. Chem. Soc. 2012, 134, 8662−8669.

(55) Gonçalves, M. S. T. Fluorescent Labeling of Biomolecules with Organic Probes. Chem. Rev. 2009, 109, 190−212.

(56) Pramanik, A.; Patibandla, S.; Gao, Y.; Gates, K.; Ray, P. C. Water Triggered Synthesis of Highly Stable and Biocompatible 1D Nanowire, 2D Nanoplatelet, and 3D Nanocube CsPbBr3 Perovskites for Multicolor Two-Photon Cell Imaging. J. Am. Chem. Soc. Au 2021, 1 (1), 53−65.

(57) Ou, X.; Liu, Y.; Lei, X.; Li, P.; Mi, D.; Ren, L.; Guo, L.; Guo, R.; Chen, T.; Hu, J.; Xiang, Z.; Mu, Z.; Chen, J.; Hu, J.; Jin, Q.; Wang, J.; Qian, Z. Characterization of Spike Glycoprotein of SARS-CoV-2 on Virus Entry and Its Immune Cross-Reactivity with SARS-CoV. Nat. Commun. 2020, 11, 1620.