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Special Collection: Microfluidic Detection of Viruses for Human Health

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INTRODUCTION AND BACKGROUND

Given the pandemic of COVID-19, the need for field- and clinic-ready diagnostic kits is in high demand. Low-cost disposable devices for virus detections on the scale are critical to minimize infection spreading in a society. Many commercial testing kits based on antigen binding are available in the market (known as rapid antigen tests),[1,2] while the challenges in rapid virus determination and quantification remain. Indeed, many lab-intensive protocols, such as virus extraction, lysis, antibody assay, and polymerase chain reaction (PCR), are required to precisely measure the virus from human specimens, including nasopharyngeal swabs, blood withdrawals, urine, or feces, while the conventional antigen binding assay with limited detection sensitivity can only be useful for certain scenarios.[3,4] In the "Microfluidic Detection of Viruses for Human Health" Special Topic in *Biomicrofluidics*, a series of emerging microfluidic strategies are introduced to offer potential new advanced diagnostic kits to detect the virus in a more timely manner. For example, microfluidic PCR technology was investigated to quantify the virus with a high sensitivity to indicate infectious disease progress. In addition, many novel chemical materials and microfluidic components are introduced here to extract the virus and related biomarkers to convert a lab-based bio-chemical analysis to a rapid point of care assay by using a low-cost integrative device.

SUMMARY OF AREAS COVERED

Carbon-based nanomaterials [including graphene and nanodiamonds (NDs)] are introduced by Xu *et al.*[5] to detect SARS-CoV-2. Carbon-based nanomaterials include carbon-based quantum dots (CQDs), carbon nanotubes (CNTs), graphene and derivatives, and nanodiamonds (NDs). They can be detected either optically or electrochemically, including field-effect transistors (FETs), and have proven to demonstrate high accuracy and low detection limit. Since the number of such demonstrations for SARS-CoV-2 was relatively small at the time of writing, the authors have also summarized the use of carbon-based nanomaterials toward MERS and SARS-CoV, the earlier variants of SARS-CoV-2.

A microfluidic approach was investigated by Huang *et al.*[6] to determine the transcriptomic biomarkers through PCR for on-site testing of COVID-19. Similar to the laboratory-based methods, microfluidic COVID-19 diagnostics can be categorized into (1) real-time PCR based, (2) DNA microarray-based, (3) microfluidic PCR, (4) antibody-based diagnosis chip, (5) aptamer-based detection chip, (6) antibody mimics-based detection chip, (7) single chip for multiple viral nucleic acid tests, and (8) gold nanoparticle enhanced immuno-PCR. Additionally, all-in-one microfluidic platforms, CRISPR-Cas12-based detection chip, on-chip isothermal amplification method [(loop-mediated isothermal amplification) LAMP and (recombinase polymerase amplification) RPA], and DNA hydrogel detection system are also explained.

Aerosol sample collection methods for on-site COVID-19 testing were summarized by Yoon *et al.*[7] While most other COVID-19 assays and biosensors were focused primarily on the detection part, particular care must also be taken for the sample preparations, which are often labor-intensive and time-consuming. Microfluidics can be utilized to automate and speed up these sample preparations, which have been demonstrated successfully for other assays. In this review, they summarized the microfluidic sample preparation methods for the isolation and purification of viral samples, including their limitations and potential future advances. Since the number of such microfluidic SARS-CoV-2 sample preparations is still relatively low at the time of writing, the authors have also summarized similar attempts of other respiratory viruses. The methods included bead-based, droplet-based, structure-based, and fluid property-based approaches.

A microfluidic device based on thermophoretic approach was developed by Ren *et al.*[8] to effectively collect aerosol from patients for on-site testing. While almost all COVID-19 assays have been conducted with human specimens, direct detection from aerosols is key for early disease monitoring. Professor Ren's group has optimized operational conditions to efficiently collect the aerosol samples toward a more rapid and accurate RNA test of SARS-CoV-2.

The microfluidic immunoassay of antibodies to quantify the immunity acquired after infection and/or vaccination was introduced by Chen *et al.*[9] By subsequently flowing the samples and detection reagents through a well-designed microchamber, a series of immunoassay can be quantitatively performed to indicate the infectious progress. The microfluidic antibody assay should consider (1) surface modification, (2) microfluidic kinetics, (3) signal output, (4) micro/nanoparticles for signal amplification, (5) sample matrix, and (6) application to detect anti-SARS-CoV-2 antibodies.

Microfluidic compartmentalization methods were summarized by Chen *et al.*[10] to identify the gene biomarkers. The samples can be confined into small microwells, or droplets, to increase the biomarker concertation, so the sensitivity can be improved significantly. Three designs were introduced: (1) microwell-based PCR platforms, (2) droplet-based PCR, and (3) point-of-care devices including centrifugal chip, SlipChip, and self-powered integrated microfluidic point-of-care low-cost enabling chip. By capturing target genes in microwells with a small sample volume ($\sim\mu$l), sensitivity can be enhanced. Additionally, with the advance of significant sample volume minimization ($\sim$pl) using droplet technology, gene quantification is possible. These improvements in cost, automation, usability, and portability have thereby allowed point-of-care applications to decentralize testing platforms from laboratory-based settings to field use against infections.

CONCLUSIONS

Through the "Microfluidic Detection of Viruses for Human Health" Special Topic in *Biomicrofluidics*, with primary emphasis on COVID-19 (SARS-CoV-2), we have provided an international discussion forum on this timely topic. Unfortunately, whether we want it or not, a new variant of coronavirus or another new form of the pathogenic virus will undoubtedly emerge in the future. However, with these improved understanding and assay tools that have developed in recent years, we will be better prepared when it arrives in the future.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Jeong-Yeol Yoon: Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Chia-Hung Chen:** Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

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