Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Science Bulletin 67 (2022) 1823–1826

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Science Bulletin
www.scibull.com

News & Views

Biochips under COVID-19: a new stage of well-grounded development and accelerated translation

Jiajia Liu [a], Youchun Xu [a,b], Jing Cheng [a,b,*]

[a] State Key Laboratory of Membrane Biology, Department of Biomedical Engineering, School of Medicine, Tsinghua University, Beijing 100084, China
[b] National Engineering Research Center for Beijing Biochip Technology, Beijing 102200, China

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed a heavy burden on the global healthcare system, especially in developing and underdeveloped countries where professionals and specialized laboratories are scarce. And due to the increased demand for large-scale detection and the shortage of animal models for vaccines and antiviral drugs under the coronavirus disease 2019 (COVID-19) pandemic, the development and translation of lab-on-a-chip (LoC) for rapid diagnosis in a self-contained environment and organ-on-a-chip (OoC) for *in vitro* study have been greatly accelerated.

Especially, the COVID-19 pandemic reaffirmed the importance of biochip platforms for diagnosis in community-based and decentralized medical systems, and greatly accelerated the translation from research to clinical application. As of April 15, 2022, 1135 SARS-CoV-2 diagnostic methods based on biochips had been authenticated by Conformitè Europëenne (CE) authentication (https://covid-19-diagnostics.jrc.ec.europa.eu/), which represents 42.2% of the total number (2689) of *in vitro* diagnostic (IVD) products for COVID-19 (Fig. S1 online). Moreover, 100 (36.4%) of 274 individual Emergency Use Authorizations (EUAs) for SARS-CoV-2 molecular diagnostic tests registered with the Food and Drug Administration (FDA) of the United States (Fig. S2 online) are for direct-to-consumer or home collection (https://www.fda.gov/medical-devices), and 27 of 104 IVD techniques registered with the National Medical Products Administration (NMPA) of China (Fig. S3 online) have been authorized for self-served testing (https://www.nmpa.gov.cn/datasearch/search-result.html). Several of these commodities generated significant contributions to the ongoing struggle against COVID-19.

Lab-on-a-chip for nucleic acid (NA) testing. Among existing diagnostic strategies, NA diagnostics are the most sensitive approaches since they enable the direct detection of specific RNA or DNA regions prior to the onset of an immune response. While traditional PCR detection of pathogens is almost impeccable in terms of sensitivity and stability, the high requirements for professionals and specialized environments impede its implementation in all regions and scenarios. To increase the accessibility of NA detection and further simplify the supporting equipment of LoC, isothermal amplification techniques, such as loop-mediated isothermal amplification (LAMP), recombinase polymerase amplification (RPA), and nucleic acid sequence-based amplification (NASBA), have been selected as substitutes for PCR [1]. Nevertheless, a typical problem exists that they may be plagued by nonspecific detection signals when combined with a conventional fluorescent dye or colorimetric readout. Consequently, clustered regularly interspaced short palindromic repeats (CRISPR) systems, particularly CRISPR/Cas12 and CRISPR/Cas13, which recognize specific target sequences at low temperatures (37 °C), have been widely utilized in LoC platforms. In addition to providing highly sensitive molecular diagnosis with the aid of isothermal amplification technology [2,3], CRISPR/Cas systems also enable performance in amplification-free NA detection, as illustrated by the following two examples. The first platform is a CRISPR/Cas13a assay-based LoC platform developed by Fozouni et al. [4] in 2021. It is capable of detecting SARS-CoV-2 directly from pre-extracted nasal swabs in 5 min with a detection limit of 500 copies/μL and has successfully identified a set of positive clinical samples. The other platform utilizes microdroplets to perform a single-molecule assay based on the CRISPR/Cas12a system, which is able to identify the African swine fever virus with excellent specificity [5]. It should be noted that the reaction system in nanoliter droplets or microwells has higher local concentrations, which could theoretically increase the detection sensitivity. Thus, by transplanting some intriguing signal amplification strategies to a small volume, such as the use of an autocatalysis-driven feedback amplification network [6], breakthroughs might be achieved in the development of an ultrasensitive LoC detection platform. In addition, regardless of whether technologies utilize isothermal amplification or CRISPR/Cas, their reagent costs are still substantially higher than those of PCR, which is an obstacle to further translation. The PCR technique itself is being continuously improved, and at present, much LoC research is still focused on the miniaturization of instruments for PCR and the rapidity of the reactions [7].

In addition to the signal amplification and detection methods discussed above, sample preparation is a critical component of the LoC platform for NA testing. However, there are only a few highly integrated platforms currently available that can enable the entire process from raw samples to readable results. A centrifugal microfluidics-based NA analyzer constructed in our previous

* Corresponding author.
E-mail address: jcheng@tsinghua.edu.cn (J. Cheng).

https://doi.org/10.1016/j.scib.2022.08.003

study [8] was capable of detecting nucleic acids of SARS-CoV-2 at concentrations as low as 150 copies/mL from the raw sample in 45 min, which is a typical product proven by NMPA that integrates the entire process for NA analysis. Nevertheless, simplifying and miniaturizing the supporting instruments and even making them non-instrumental remains a challenge to a fully integrated platform. Considering the "ASSURED" standard proposed by the World Health Organization, a qualified point-of-care (POC) device should have the following attributes: affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end users. Thus, the development of the LoC platform for NA diagnosis with increasing standards would continue to be a future trend.

Lateral flow chip and microarrays for protein examination. Although not as sensitive as NA detection for the early diagnosis of viral infections, immunoassays based on the recognition of viral antigens or antibodies generated by the host's immune system can easily achieve low-cost, high-throughput, and multitarget testing. Two typical examples of biochips for protein examination are the rapid COVID-19 antigen home testing strip (lateral flow chip) and the SARS-CoV-2 proteome microarray [9]. In particular, the strips present qualitative results, whereas proteome microarrays yield quantitative data that enable a comprehensive analysis of the humoral immune response to SARS-CoV-2 and further progress towards developing antibody-based diagnostics and therapeutic processes. Hence, biochips for protein examination serve as a vital supplement to NA testing for clinical application, as they enable the identification of prior viral infection, evaluation of humoral immunity, and promotion of epidemiological and vaccine studies. In addition to their use in pandemic prevention and control, a significant number of biochip platforms for proteins are still focused on understanding the relationship between mRNA and protein at the molecular level, as well as quantifying low-abundance proteins as biomarkers. Currently, a major analytical challenge for protein chips is how to pretreat biological samples, minimize cross-contamination, and measure multiple targets in a complex matrix with both high sensitivity and a wide dynamic range.

Lab-on-a-chip for biochemical detection. Chronic diseases have been spreading rapidly over the past few decades as a result of deteriorating environmental conditions and unhealthy lifestyles. The high correlation between COVID-19 mortality rates and chronic illnesses significantly exacerbates the current situation of patients, and subsequent disease management also faces a variety of unexpected problems. On one hand, bulky protective clothing and fogging goggles make it extremely difficult to complete venous blood collections in isolation wards, especially in intensive care units (ICUs), which not only adds to the workload of medical professionals but also makes patients suffer from venepuncture errors. On the other hand, the limited supply of medical resources makes it difficult for chronic patients who require frequent biochemical monitoring. A fully integrated LoC platform that is capable of performing multiple biochemical analyses would be an ideal option to address these issues. In a previous report [10], we presented an LoC platform that allowed for the measurement of glucose (GLU), total cholesterol (TC), and triglyceride (TG) levels in approximately 15 min with only 12 μL of fingertip blood, and this platform has now been extended to provide the detection of liver function and renal function indicators. Once used in ICU, the aforementioned LoC system not only greatly reduces the workload of medical professionals and the suffering of the patients, but also significantly shortens the reporting time. However, restricted by the miniaturization of instruments and the simplification of biochips, the reagents used in high throughput analyzers are often not readily adaptable to the LoC platform, resulting in a long iterative cycle of detective indicators. The use of new strategies adapted to the LoC platform, such as the incorporation of multiple driving forces and the introduction of new reaction principles, is crucial to increasing the versatility of portable biochemical analyzers.

Organ-on-a-chip for therapeutic research. The OoC systems are becoming emerging models designed to reduce, replace, and refine (3Rs) the use of animal models and provide improved prediction of human responses *in vitro* due to the absence of species-specific effects. Essentially, OoC represents partial functions of organs, such as the transport function of a blood vessel, the barrier function of a lung, or the filtration function of a kidney, rather than modeling their entire functionality. Compared to cultured 2D cells, tissues, or statically grown 3D organoids, OoC platforms replicate the smallest functional tissue units of the body in terms of three key characteristics: the structured arrangement of tissues or cells, the combination of multiple cell types to achieve physiological balance, and the presence of biomechanical forces to mimic the microenvironments of cells. Nevertheless, exclusively pursuing higher biological fidelity may lead not to better functional performance but to higher costs in both time and money. "How simple is complex enough?" This is a long-standing question that has needed to be addressed in this field since 2010.

It has been reported that the predominant receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), which is widely present in human cells. Consequently, many organs are involved in both the acute initial infection stage and the post-acute infection stage (known as long COVID-19) of COVID-19 [11], such as the lung (pneumonia), stomach and intestine (diarrhea), heart (myocarditis), pancreas (new-onset hyperglycemia), liver (hyperbilirubinemia), vessels (coagulopathy), and eye (conjunctivitis). Fortunately, OoC was developed to model a broad range of human disorders and diseases covering virtually all organ systems before the COVID-19 outbreak. The accumulated experience provides a great deal of assistance in the application of OoC in COVID-19 studies and can contribute to new insights regarding antiviral therapeutics and prophylactics [12,13].

Although we all wish to see the rapid translation of technology to application, the inherent technical hurdles presented faced by OoC platforms still need to be overcome. Despite adding a spatial component to 2D cultures, many available OoC platforms are referred to as 2.5D models since they consist of a limited number of cell types and are not fully encapsulated as in 3D cultures. Due to the ability to create cell phenotypes that more closely resemble native tissues, 3D bioprinting, 3D scaffolding, and 3D organoid cultures offer more optimized synergistic technologies than sequential cell seeding in the development of OoC platforms [14]. Moreover, comprehensive systemic complications and sequelae of SARS-CoV-2 infection have been continually reported, underscoring yet again that a single OoC model is inadequate to examine the interactions among different organizations and viruses. Nonetheless, when attempting to connect different organ models to a multi-OoC platform, there is a fundamental issue that the modeling of parenchymal tissue function and physiological barrier function requires different engineering and perfusion strategies. Specifically, parenchymal tissue function is modeled through 3D culture methods using a single perfusion line, and physiological barrier function is modeled by cultivating different types of cells on different sides of a porous membrane using two independent perfusion lines. The integration of immune and endocrine systems into multi-OoC and single OoC platforms is also a critical issue that has been made more pressing by the inability to model disease-immune-endocrine interactions in animal models. Furthermore, the increased complexity of the system suggests higher requirements for monitoring technologies, namely, real-time, *in situ*, and long-term ongoing sensing and monitoring, which are needed to solve the problems of saturation and regeneration of the sensors.

Ideally, diagnostic biochips are supplements or even substitutes for centralized detection, as they have the advantages of equip-

ment miniaturization, process integration, and detection automation through the use of microfluidic technology, and are capable of performing rapid and accurate POC testing. However, most commercial biochips for diagnosis are simply practiced on the simulation or miniaturization of traditional approaches or detection instruments. Although LoC platforms based on electrochemical sensors, chemiluminescence sensors, magnetic sensors, optical fiber sensors, and other technologies are active in using novel materials and new detection strategies, enabling fast and sensitive pathogen detection, they still fail to meet the criteria for commercialization due to unsolved problems such as stability and portability (for a more detailed discussion see Supplementary materials online). Therefore, developers of next-generation biochips for diagnosis, especially the new LoC platforms, should be concentrating on the integration of mature technologies. As the world is moving from pandemic response to pandemic control and focusing on economic recovery, the most critical factor in deploying the POC platforms, especially those biochip-based ones, is the control of the prime cost. It may include the selection of inexpensive materials, the optimization of the reaction processes, the reduction in reagent costs, as well as the simplification of instrument components and mass production.

Although OoC is still in its infancy and there are many limitations and challenges, it can still be utilized as an alternative model for current drug development and pathological research. Public data indicate that major pharmaceutical manufacturers, including Hoffmann La Roche, AstraZeneca, Novartis, Pfizer, Hengrui Medicine, and Simcere, have been using organ chips to simulate *in vitro* tests. However, to accelerate commercial translation, it is crucial to resolve challenges such as large-scale cell production, effective cell transplantation, and repeatable batch construction of OoC by advancing bioengineering methods.

In this paper, we provide a brief review of recent studies and advances related to the biochip field under COVID-19. An overview

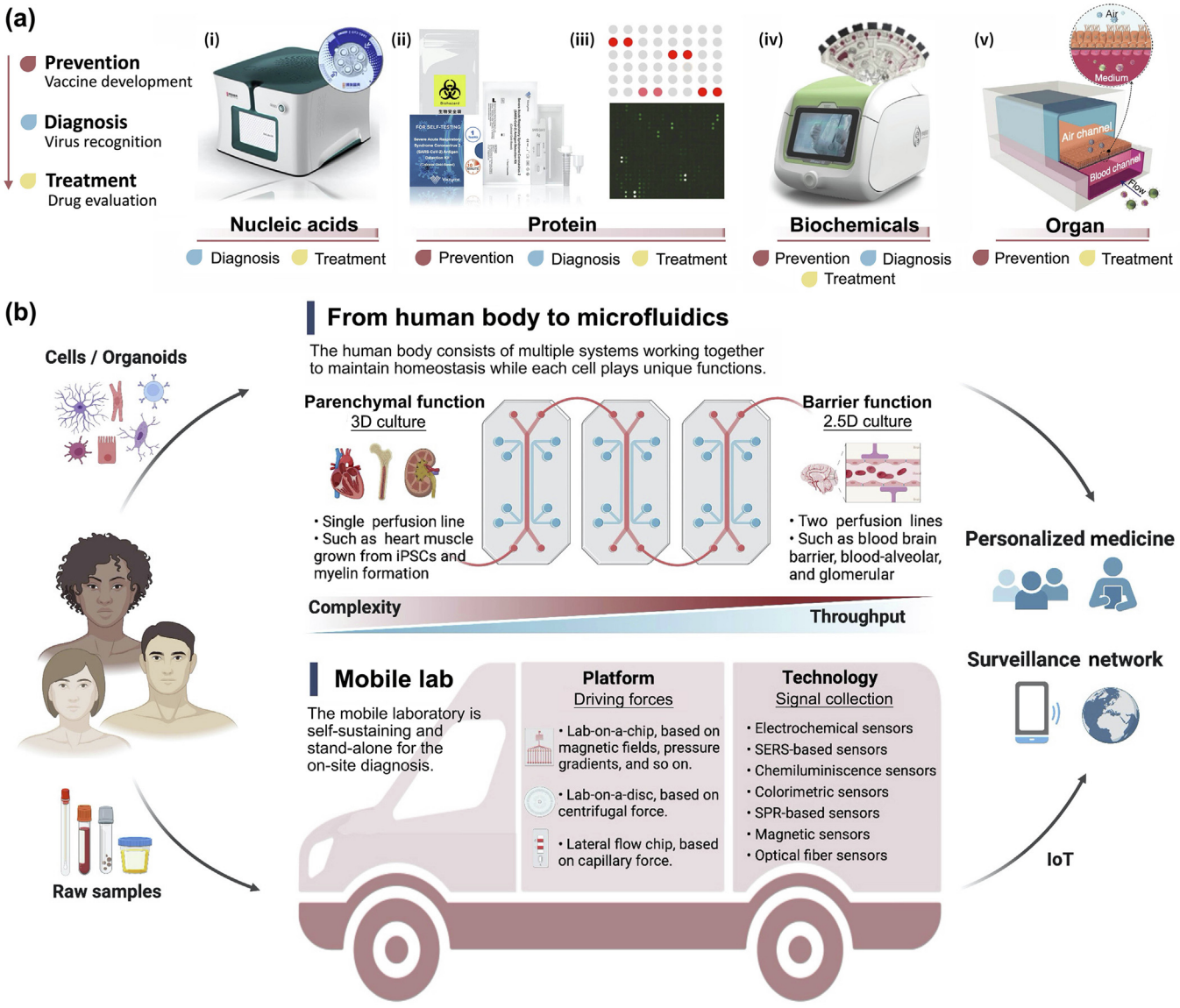

Fig. 1. Overview of the biochip platforms. (a) Representative biochip platforms applied to the prevention, diagnosis, and treatment of COVID-19. From left to right, the picture illustrates (i) a fully integrated LoC system for NA detection of SARS-CoV-2 (CapitalBio Technology, China) [8], (ii) a SARS-CoV-2 antigen detection kit based on colloidal gold for self testing (Vazyme, China), (iii) a peptide-based proteome microarray for providing fundamental insight into humoral immunity during SARS-CoV-2 infection [9], (iv) a fully integrated microfluidic analyzer for performing multiple biochemical analyses with fingertip blood [10], and (v) a human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics [13]. (b) Diagnostic and therapeutic systems based on microfluidic chips (created with BioRender.com). iPSCs, induced pluripotent stem cells; IoT, Internet of Things; SERS, surface-enhanced Raman scattering; SPR, surface plasmon resonance.

of the biochip platforms is shown in Fig. 1. Additional detailed descriptions of microfluidic systems design and materials of biochips, as well as the various organ chip models that have been developed before, can be found in the published reviews [15,16]. To promote lab-to-field transition of biochips, the following issues should be addressed (for a more detailed discussion see Supplementary materials online): (1) establishing industry standards for production and market supervision; (2) developing cloud computing platforms for POC device support; (3) policy support and promotion. Once the community-based testing is scaled up, intelligent monitoring networks will be established to benefit not only the surveillance of newly emerging epidemics but also the development of personalized medicine based on the Internet of Things.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (31870853 and 82161138004), Guangzhou Institute of Respiratory Health Open Project (funds provided by China Evergrande Group, 2020GIRHHMS02), Emergency Key Program of Guangzhou Laboratory (EKPG21-14), Tsinghua University Spring Breeze Fund (20201080532), Beijing Nova Program 2020, and Beijing Lab Foundation.

Appendix A. Supplementary materials

Supplementary materials to this news & views can be found online at https://doi.org/10.1016/j.scib.2022.08.003.

References

[1] Xing W, Liu Y, Wang H, et al. A high-throughput, multi-index isothermal amplification platform for rapid detection of 19 types of common respiratory viruses including SARS-CoV-2. Engineering 2020;6:1130–40.
[2] Joung J, Ladha A, Saito M, et al. Detection of SARS-CoV-2 with SHERLOCK one-pot testing. N Engl J Med 2020;383:1492–4.
[3] Wang X, Zhong M, Liu Y, et al. Rapid and sensitive detection of COVID-19 using CRISPR/Cas12a-based detection with naked eye readout, CRISPR/Cas12a-NER. Sci Bull 2020;65:1436–9.
[4] Fozouni P, Son S, Diaz de Leon Derby M, et al. Amplification-free detection of SARS-CoV-2 with CRISPR-Cas13a and mobile phone microscopy. Cell 2021;184:323–33.
[5] Yue H, Shu B, Tian T, et al. Droplet Cas12a assay enables DNA quantification from unamplified samples at the single-molecule level. Nano Lett 2021;21:4643–53.
[6] English MA, Gayet RV, Collins JJ. Designing biological circuits: synthetic biology within the operon model and beyond. Annu Rev Biochem 2021;90:221–44.
[7] Khodakov D, Li J, Zhang JX, et al. Highly multiplexed rapid DNA detection with single-nucleotide specificity via convective PCR in a portable device. Nat Biomed Eng 2021;5:702–12.
[8] Xing W, Wang J, Zhao C, et al. A highly automated mobile laboratory for on-site molecular diagnostics in the COVID-19 pandemic. Clin Chem 2021;67:672–83.
[9] Cheng L, Zhang X, Chen Y, et al. Dynamic landscape mapping of humoral immunity to SARS-CoV-2 identifies non-structural protein antibodies associated with the survival of critical COVID-19 patients. Signal Transduct Target Ther 2021;6:304.
[10] Zhu Y, Meng X, Chen Y, et al. Self-served and fully automated biochemical detection of finger-prick blood at home using a portable microfluidic analyzer. Sensors Actuators B Chem 2020;303:127235.
[11] Han Y, Yang L, Lacko LA, et al. Human organoid models to study SARS-CoV-2 infection. Nat Methods 2022;19:418–28.
[12] Goyal G, Prabhala P, Mahajan G, et al. Ectopic lymphoid follicle formation and human Seasonal influenza vaccination responses recapitulated in an Organ-on-a-Chip. Adv Sci 2022:e2103241.
[13] Si L, Bai H, Rodas M, et al. A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics. Nat Biomed Eng 2021;5:815–29.
[14] Karzbrun E, Khankhel AH, Megale HC, et al. Human neural tube morphogenesis in vitro by geometric constraints. Nature 2021;599:268–72.
[15] Wang C, Liu M, Wang Z, et al. Point-of-care diagnostics for infectious diseases: from methods to devices. Nano Today 2021;37:101092.
[16] Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nat Rev Genet 2022:1–25.

Jiajia Liu is a Ph.D. candidate at School of Medicine, Tsinghua University. Her research focuses on biochip-based rapid diagnosis of infectious diseases utilizing CRISPR/Cas system.

Jing Cheng is a Professor at School of Medicine, Tsinghua University. His research interest is in the field of biotechnology, in particular in the area of biochips. As Director of the National Engineering Research Center for Beijing Biochip Technology, he has established a series of biochip-based molecular typing systems for disease prevention, diagnosis, and prognosis and has committed to building a comprehensive health management platform by involving traditional Chinese medicine.