



# Chemical Translational Biology-Guided Molecular Diagnostics: The Front Line To Mediate the Current SARS-CoV-2 Pandemic

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The spread of severe respiratory syndrome coronavirus 2 (SARS-CoV-2) has disrupted our global society in unprecedented ways. The very front line in defense against this pandemic is molecular diagnosis, which is an exceptional representation of how chemical translational biology can benefit our lives. In this viewpoint, I emphasize the imperative demand for a simple and

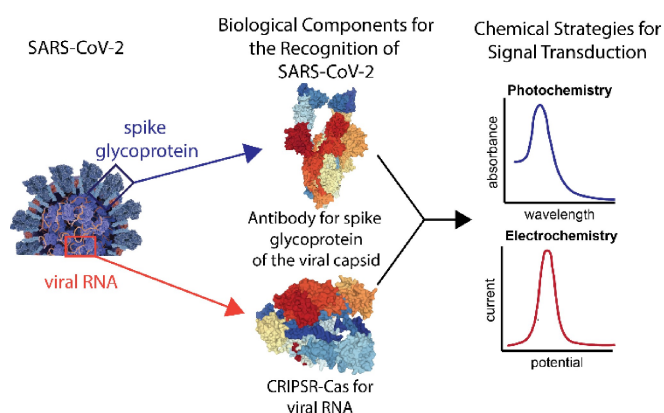
rapid point-of-care system in order to mediate the spread of COVID-19. I further describe how the interdisciplinary combination of chemistry and biology advances biosensing systems, which potentially lead to integrated and automated point-of-care systems capable of relieving the current pandemic.

Nature's great repository provides us with a wide diversity of biological tools, granting us various incredible capabilities to address complex scientific problems, many of which create the foundations of a better society through translationally focused research tailored by chemical strategies mediated biological systems. At the current time, the global community is facing unprecedented disruption from the coronavirus disease 2019 (COVID-19) pandemic,<sup>[1]</sup> which actually brings the significance of chemical translational biology into focus.

In response to the outbreak of the COVID-19, the very front line to intervene against the propagation of this lethal virus is molecular diagnosis,<sup>[2]</sup> which is an eminent translational research representation produced by the integration of chemistry and biology. SARS-CoV-2, as a RNA virus, is typically tested by performing real-time reverse transcriptase-polymerase chain reaction (RT-PCR) on samples processed from patients' nasopharyngeal swabs to determine the copies of the viral RNA.<sup>[3]</sup> However, the operation of RT-PCR for RNA virus detection requires multiple-step sample processing with central lab facilities, which significantly reduce the turnaround time when encountering large quantities of tests needed. Just as the U.S. is currently facing, with a large quantities of potential patients, the waiting time for test results has been increased from days to weeks, which can delay individual treatment and ultimately, increase the mortality rate of the community.<sup>[4]</sup> Therefore, a simple and accurate point-of-care device that can identify SARS-CoV-2 rapidly with a simple signal transduction system is highly desirable.<sup>[5]</sup> Recent technological breakthroughs in molecular diagnosis based on chemical biology principle actually fulfill this need.

The development of molecular diagnostic science demonstrates a combined effort from both chemistry and biology with a potential translational outcome, such as a point-of-care biosensing device. The construction of a typical biosensing system is necessarily composed of two fundamental elements, a recognition element and a transduction element (Figure 1).<sup>[6]</sup> A recognition element uses the recognition capability of naturally evolved biomolecules, such as antibodies and RNA-guided CRISPR Cas systems, to sense target biomolecules.<sup>[7]</sup> A transduction element functions to translate biomolecular recognition activity into a physicochemical signal through electrochemistry or photochemistry.<sup>[8]</sup> A significant effort has been made to design and integrate these two elements in order to provide a sensitive, cost-effective, and time-efficient biosensing system, potentially helping our society to combat the current life-threatening issue.<sup>[9]</sup>

Very recently, the Sherlock CRISPR SARS-CoV-2 kit became the first CRISPR-based diagnostic device approved by the U.S. FDA emergency use authorization (EUA) for the detection of SARS-CoV-2 RNA.<sup>[10]</sup> This system employs the high-accuracy



**Figure 1.** A typical biosensing system is composed of a biomolecular recognition element and a chemical-strategy-guided transduction element.

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gene editing tool, CRISPR, as the recognition element,<sup>[7,11]</sup> which provides programmability toward any desired nucleic acid target as a modular component. Depending on the Cas13's trans-cleavage activity on the reporter nucleic acid upon detection of a specific target,<sup>[12]</sup> this assay integrates into a lateral flow paper strip on which biomolecules that can bind the reporter strands are immobilized. The gathering of the reporter strands on the testing strip results in the aggregation of gold nanoparticles, which leads to a visualizable color change,<sup>[13]</sup> similar to a pregnancy test. This characteristic example demonstrates the empirical design logic of molecular diagnostic systems. First, a biological unit functions as a sensor and actuator, which is activated by a specific target cue. Second, a chemical strategy that can acquire the information actuated by the biological unit generates a physicochemical signal enabling downstream processing and quantification. For the biological unit, genetic engineering and computational design tools allow de novo construction of biomolecules with desired functionalities, expanding the capabilities to sense any molecules of interest.<sup>[14]</sup> Moreover, advancements in DNA nanotechnology provide us with capabilities on programmable designs of DNA circuits to deliver versatile functions benefiting sensing performance,<sup>[15]</sup> such as hybridization chain reaction for signal amplification,<sup>[16]</sup> primer exchange reaction for translation,<sup>[17]</sup> and strand displacement for circuit computation.<sup>[18]</sup> The integration of various types of functional biomolecules contributes target specificity, programmability and modularity to the biosensing system, furnishing a possibility for the development of a universal biosensor. With regard to the chemical strategy for signal generation, electrochemistry and photochemistry allow the use of chemically synthesized organic molecules to transduce the biomolecular recognition event into electrical and optical signals.<sup>[19]</sup> For example, electrochemical biosensors use redox reactions to initiate electron transfer on an electrode. The target biomolecule capturing event on the sensor can change the rate of electron transfer on the electrode surface, achieving quantification through electrical current.<sup>[20]</sup> Also, the use of FRET paired fluorophores for photochemical biosensors can directly probe the structure change of the recognition element upon the binding of a target molecule,<sup>[21]</sup> realizing real-time sensing. Concluding from above demonstrations, it is clear that the construction of an integrated point-of-care system relies on an inevitable combination of a biological unit and a chemical transducing strategy, highlighting the paramount importance of chemical translational biology on the development of point-of-care systems to

mediate the current global crisis. With established fundamental aspects of biorecognition elements and chemical transducing strategies, future researches can aim to engineer better integration strategies toward automated and universal biosensors suitable for mass production, progressing closer to the gold standard established by the commercialized glucose sensor. These potential advancements can provide powerful tools toward preventing emerging infectious diseases in the future.

Scientific and technological advances in chemical biology have equipped our society with better methods and devices to deal with the current pandemic. However, it is also extremely critical for us, communities as a whole, to realize the fatality of community transmission and protect ourselves and our families with proper equipment. Let's work together and the old normal will be back.

### Conflict of Interest

The author declares no conflict of interest.

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Yifan Dai received his B.S. and Ph.D. degrees from Case Western Reserve University in chemical and biomolecular engineering. He joined the Department of Biomedical Engineering in Duke University as a post-doc associate. His research areas include the construction of bio-electrochemistry interfaces for biomolecular analysis and developments at the interface of protein engineering and synthetic biology.

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