



Nanozymes to fight the COVID-19 and future pandemics

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In 2019, the pandemic induced by the rapid spread of the severe acute respiratory syndrome coronavirus-2 'SARS-CoV-2', also named coronavirus disease 'COVID-19', has rapidly caused serious health, economic, social, and political issues worldwide. This has been accentuated by asymptomatic carriers, fast viral mutations, incoherent lockdown policies, and limited methods of detection and treatment. Nucleic acid tests for COVID-19 are lengthy and complicated, and the rapid antibody tests produce false-negative diagnoses, particularly in the early stage of infection. Moreover, there are no specific and effective medicines available for treatment. Therefore, rapid diagnostics and therapeutics are urgently required. Here, we argue that nanozymes—enzyme-mimicking nanoparticles—could be used for faster, more sensitive, and accurate detection and treatment of the COVID-19. Indeed, nanozymes have high surface areas allowing easier bioconjugation for detection, and nanozymes possess integrated drug-functionalization for treatment. Moreover, the size, composition, and surface chemistry of nanozymes can be rationally designed for improved therapeutic applications.

COVID-19 history

The COVID-19 appeared in Wuhan, China, due to emergence of a novel strain of coronavirus (Sallard et al. 2021), which was provisionally named '2019-nCoV' by the World Health Organization (WHO). Later, the virus was renamed 'SARS-CoV-2' by the International Committee

on Taxonomy of Viruses based on the phylogeny and taxonomy (Gorbalenya et al. 2020). Genetic analysis has confirmed the resemblance of the key genes of SARS-CoV-2 with other coronaviruses causing respiratory diseases (Zhou et al. 2020). Further, the genes of SARS-CoV-2 are undergoing frequent mutations, and several new variants have been reported: B.1.351 in South Africa, B.1.1.7 in the UK, B.1.427 and B.1.429 in the USA, and B.1.617 in India (Kemp et al. 2020). Moreover, a new strain S-614G showing increased replication, transmission and survival following a D614G substitution was recently identified (Zhou et al. 2021).

Due to rapid mutations, SARS-CoV-2 is displaying higher pathogenicity and virulence compared to previous strains, namely the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS-CoV2, Paliwal et al. 2020). The rapid air transmission of the virus has induced the contagious spread, leading to the ongoing pandemic. This pandemic has been amplified by the potency of the virus to remain viable on surfaces for several hours, and in some cases several days (Sharma et al. 2020). The major symptoms of COVID-19 are variable, and the patients may have fever, headache, cough, fatigue, loss of smell and taste or breathing difficulties. After recovery, some patients still experience various adverse effects, including damage to organs due to inflammation, hypercoagulability, endothelitis, vasoconstriction or oedema (Jain 2020). Since there is no effective and specific treatment for infected cases, prevention and vaccination are actually the sole means to control the pandemic.

Prevention and treatment

Numerous and sometimes contradictory policies have been issued by nations and health agencies to reduce transmission from infected persons to healthy individuals (Fig. 1). Policies include physical distancing of two meters, frequent hand washing, and personal hygiene, according to the US Centre of Disease Control and Prevention (CDC). These

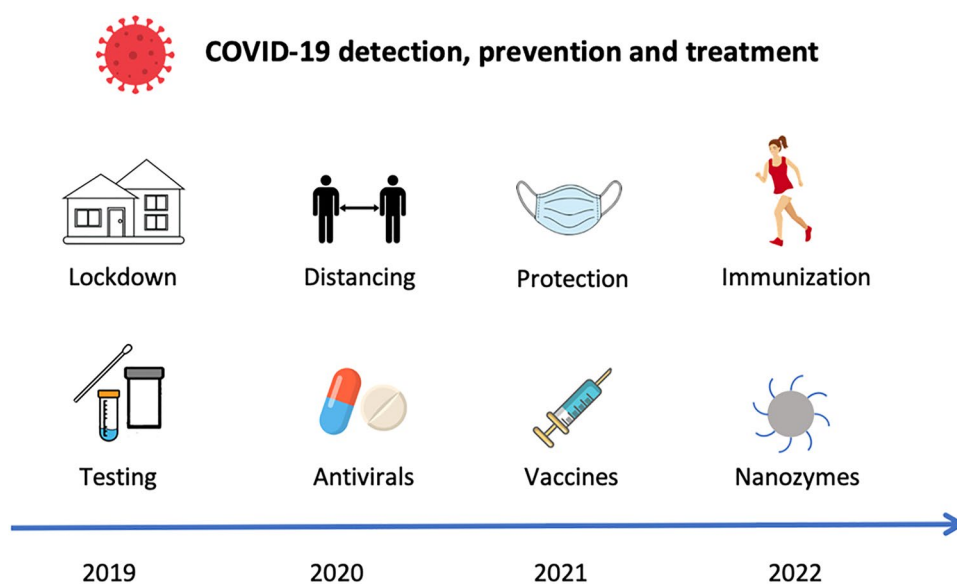
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Fig. 1 Approximate history of policies and means taken to decline the COVID-19 pandemic. Nanozymes are actually promising for detection, disinfection and treatment. Nanozymes are artificial enzymes made with nanomaterials (https://en.wikipedia.org/wiki/Artificial_enzyme)



recommendations are based on respiratory studies carried out in 1930s (Shope 1931; Smith et al. 1933). Self-isolation has also been advocated for COVID-19 patients or infected suspects. Health agencies have provided directives for self-isolation and strict self-quarantine instructions to high-risk groups. Another policy was the use of personal protective equipment such as masks and respirators, in particular by healthcare professionals. Face coverings with masks are advised, in particular when social distancing is challenging to maintain, e.g. in transportations.

Lockdown has also been imposed in many countries, yet strict lockdown of groups and families in densely populated cities has probably favoured viral transmission within families. In other words, lockdown has sometimes concentrated the population, and this is contradictory to physical distancing. In addition, ventilation and air filtration in hospitals and other public buildings have been recommended to clear out infectious aerosols. Lastly, improving immunity by eating nutritious food, doing daily physical activity, stress management and enough sleep are advised (Ibarra-Coronado et al. 2015; Dai et al. 2021). All these practices have found to be effective in controlling viral dissemination to some extent. Nonetheless, timely detection and specific medications are urgently needed.

Limits of actual diagnostics

Early diagnosis of any disease is crucial for an appropriate treatment, yet actual testing methods to identifying SARS-CoV-2 are limited. Table 1 compares diagnostic techniques which are currently applied for COVID-19 detection (Chakraborty et al. 2020). Here, it is challenging to develop

effective diagnostics and therapeutics against SARS-CoV-2 due to the lack of validated biomarkers, frequent mutations, and unknown functional mechanisms of the virus (Paliwal et al. 2020). Nevertheless, diagnostic instrumentation such as single-photon emission computed tomography (SPECT) could be explored to diagnose the SARS-CoV-2 (Zavaleta et al. 2018). Several techniques such as L-surface plasmon resonance (LSPR) or field effector transition-based biosensing are available for detecting the viral load (Qiu et al. 2020; Seo et al. 2020). Similarly, there are few tests based on the molecular, immunological, clustered regularly interspaced short palindromic repeats (CRISPR) or serological methods with limit of detection ranging from 10 copies/ μL to 100 copies/mL.

Specific methods based on quantitative fluorescence polymerase chain reaction (QF-PCR) or isothermal nucleic acid amplification have also been developed (Bustin and Nolan 2020; Varlamov et al. 2020). Nucleic acid amplification tests (NAAT) are highly recommended by the World Health Organization, and they are based on reverse transcription-polymerase chain reaction (RT-PCR). However, nucleic acid-based testing is time-consuming and complicated, and host antibodies-based serological testing may lead to false-negatives during the initial viral infection. Moreover, paper-based testing is restricted to point-of-care testing due to the lower precision of detection. Paper-based tests include Feluda, E25Bio, and direct antigen rapid test (DART).

Table 1 Available diagnostic methods for the detection of the coronavirus disease that has appeared in 2019 (COVID-19), their principle, assay time, advantages, constraints, and detection limits. Reprinted with permission from Chakraborty et al. (2020) under the Creative Commons Attribution License (CC BY)

Method	Principle	Assay time	Advantage	Limitation	Detection limit
Reverse transcription polymerase chain reaction (RT-PCR)	Primer and fluorescent marker based	3–4 h	Reliable, detects current viral infection	Requires sophisticated instrumentation, and cannot detect already recovered patients	100 copies/mL
Reverse transcription loop-mediated isothermal amplification (RT-LAMP)	Primer-based, two to three pairs of primer can be used	2–3 h	Highly sensitive, conducted at constant temperature of 60–65 °C	Optimizing the primer and sample run	80 copies of viral RNA/mL sample
Clustered regularly interspaced short palindromic repeats (CRISPR)-based assay	Gene editing	1 h	Highly sensitive, low-resource settings	Many CRISPR kits are in the development stage and need more clinical validation	RT-LAMP/ Cas 12.10 copies/ μ l input
Serological assay, enzyme-linked immunosorbent assay, neutralizing, chemiluminescent immunoassay	Antigen–antibody based	30 min–4 h	Sensitive or good specificity	Depends on host antibody response, false positive	Enzyme-linked immunosorbent assay—5 IU/mL
Nanoparticle-based methods: gold nanoparticles, graphene oxide	Gold nanoparticles-nucleic acid hybridization via thermoplastic heating: graphene oxide-field effect transistor	Not specified	High specificity and sensitivity	Requires expertise in nanoparticle synthesis and sensor fabrication	Gold nanoparticles -0.22 pM: graphene oxide—1 fg/mL

Preanalytical bias

Another issue is the preanalytical bias, which includes difficulties to scale-up, purify, store samples and to select the best body location from which the sample is collected. Indeed, biases have been observed for 93% of samples of bronchoalveolar lavage fluids, 72% for sputum, 63% for nasopharyngeal swabs, 46% for fibrobronchoscope brush biopsy, 32% for pharyngeal swabs, 29% for stools and 1% for blood, making the site of collection of high importance (Wang et al. 2020a, b). In addition, samples may be collected before development of the viral load, thus escaping detections. Overall, low viral loads and inappropriate specimen collection may give false results, and each technique has a different limit of detection. To conclude, a rapid, sensitive, and effective diagnosis strategy is urgently required.

Variants complicate detection and treatment

COVID-19 variants are formed under selective pressure in the convalescent plasma therapy, thus inducing the rapid development of antibiotic-resistant mutations (Kemp et al. 2020; Dai et al. 2021). Selective pressure is a natural phenomenon in which the drug-survived COVID-19 variants pass on the resistant gene to the subsequent generation, whereas the drug-susceptible variants perish and do not produce offspring. Due to the process of the selective pressure, the newer COVID-19 variants show higher pathogenicity and virulence. Consequently, the actual therapeutic strategies are based on drug repositioning or drug repurposing, which encompasses scrutinizing available drugs for new therapeutic purposes. Moreover, though drugs such as remdesivir, hydroxychloroquine and chloroquine have been approved, their mechanism of action against COVID-19 remains unclear. In such a complicated scenario, rapid testing and isolating COVID-19 positive cases could prevent progression of COVID-19. Moreover, scientific characterization and identification of different COVID-19 variants should reduce the prescription of antibiotics or antivirals and, in turn, diminish antibiotic resistance. Lastly, it is noteworthy that medical diagnosis generally guides the choice of the therapy. Therefore, the lack of effective diagnostics of different variants has highly challenged the management of the pandemic.

Why nanomaterials are highly relevant?

Viruses and nanomaterials have similar dimensions, of about 20–300 nm for the most studied viruses and 1–100 nm for nanomaterials (Singh et al. 2017). Since

viruses possess designed strategies to infect all living organisms, scientists have been inspired by viruses to design nanomaterials, in particular for targeted drug and gene delivery (Wen and Steinmetz 2016). In particular, it has been predicted that nanotechnology-based pharmaceutical formulations could be powerful to limit the COVID-19 pandemic (Campos et al. 2020; Khan et al. 2021; Rangayasami et al. 2021). Nanoparticles can be tailored for prevention, diagnosis and treatments of the COVID-19 (Vahedifard and Chakravarthy 2021). Concerning prevention, colloidal solutions of silver, copper or zinc nanoparticles can be used as disinfectant, and gold nanoparticles can be designed for rapid detection of the coronavirus. Similarly, plastics containing antimicrobial silver nanoparticles, graphene or carbon nanotubes provide better safety to healthcare workers or healthy individuals.

Concerning diagnosis, nanoparticles can be used for biomarker-based, single-cell tracking because nanoparticles may have enzymatic and electric properties, chemical stability, and surface plasmon resonance (Navya and Daima 2016; Umapathi et al. 2018; Navya et al. 2019). In particular, enzyme-like properties can be fine-tuned for virus detection, drug or gene delivery, and even to impart therapeutic potentials against SARS-CoV-19. Concerning treatments, effective nanomedicines can be formulated to cure COVID-19 patients. For instance, a lipid nanoparticle-encapsulated mRNA-based vaccine has already been developed against SARS-CoV-2 to prevent secondary adverse effects of vaccines (Baden et al. 2020). Moreover, conventional issues of targeting, pharmacokinetics and compartmentalisation can be solved through tailored nanoparticles (Varahachalam et al. 2021). For example, nanoparticles used as drug carriers can decrease the toxicity of raw active substances such as zidovudine, dapivirine or efavirenz antivirals (Cojocaru et al. 2020).

Nanozymes can be tuned for biomedical applications

Nanoparticles bearing enzyme-like characteristics are named ‘nanozymes’ or ‘artificial enzymes’ (https://en.wikipedia.org/wiki/Artificial_enzyme). They have found applications for the detection of metal ions, small biomolecules, and cancer cells (Sharma, et al. 2014; Wang et al. 2020a, b; Daima et al. 2021). Nanozymes display several advantages over natural enzymes. Nanozymes can be easily manufactured and stored for longer periods, they are cost-effective and recyclable, whereas natural enzymes are often highly biodegradable and sensitive to heat, pH and pressure (Daima 2013; Daima 2014; Shankar et al. 2015; Sanjana et al. 2019). Moreover, nanozymes exhibit larger surface areas allowing

easy bioconjugation, surface modification and integrated multi-functionalization, which are not possible using natural enzymes or small chemical catalysts. Due to their size, composition and surface corona activity, nanozymes can be tuned for specific biomedical applications just by varying their size, composition and surface chemistry (Matur et al. 2020), as detailed below.

Nanozymes for detection of chemicals, viruses and cells

Nanozymes can be used for detection. For instance, cerium oxide nanoparticles are used to monitor superoxide dismutase- and catalase-mimic activities, whereas ferric-based nanoparticles detect peroxidase- and oxidase-mimic actions (Yang et al. 2017; Bhagat et al. 2018). Nanomaterials have been used for the detection of glucose, cholesterol, organophosphorous neurotoxins, DNA, c-reactive proteins, viruses, stem cell, and cancer cells (Liang et al. 2013; Maji et al. 2015; Nirala et al. 2018; Jansman and Hosta-Rigau 2019; Sun et al. 2020; Gupta et al. 2021). Signals are detected and imaged using properties such as electrochemical, chemiluminescence, fluorescence, calorimetry, surface plasmon resonance and thermoplasmonic. Platinum-based nanomaterials show pH- and temperature-dependent enzyme-mimetic behaviour, and manipulating their size, shape, surface chemistry and surface charge allows to improve their medicinal potency.

Gold nanoparticles have been explored to detect mumps and zika virus (Hsu et al. 2020; Long et al. 2020). Gold nanozymes have been employed in rapid detection of SARS-CoV-19 (Pramanik et al. 2021). Indeed, samples taken in positive patients contain nucleocapsid phosphoprotein oligonucleotides that combine with thiol-functionalized gold nanozymes, which allow detection in 10 min by calorimetry (Kamaraj 2020). Compared to the traditional calorimetric methods using natural enzymes such as horseradish peroxidases and alkaline phosphatase, nanozymes display better sensitivity by involving chromogenic and fluorogenic substrates such as 3,3',5,5'-tetramethylbenzidine, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid, 3-(4-dihydroxy phenyl) propionic acid, and 2,3-diaminophenazine. Rapid and sensitive chemiluminescence kits have been developed to detect the virus spike proteins using a Co-Fe@hemin-peroxidase nanozyme at levels of 0.1 ng/mL (Liu et al. 2020). Furthermore, the use of magnetic iron oxide nanoparticles at the pre-diagnosis stage should help to isolate viruses specifically with a magnet (Jindal and Gopinath 2020).

Nanozymes for treatment

Nanozymes can be functionalized for therapeutic purposes. For instance, virus mitochondrial proteins can be degraded by multivalent silver nanozymes (Vahedifard and Chakravarthy 2021). The silver ions bind to the RNA viral genome to activate the mitochondrial proteins exhibiting an anti-viral effect (Galdiero et al. 2011). Gold nanozymes have the ability to mimic the binding receptor of viruses, thus leading to viral deformation (Huang et al. 2019). Zinc oxide nanozymes are also able to reduce viral infection by boosting T cell and antibody-mediated response (Antoine et al. 2012; Tabish and Hamblin 2020). Overall, nanozymes appear as an effective alternative to detect and target coronaviruses, yet catalytic mechanisms are poorly known, requiring research in nanotechnology, computational engineering, machine learning, artificial intelligence, and informatics.

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