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REVIEW

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Quantum dots as a promising agent to combat COVID-19

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Approximately every 100 years, as witnessed in the last two centuries, we are facing an influenza pandemic, necessitating the need to combat a novel virus strain. As a result of the new coronavirus (severe acute respiratory syndrome coronavirus type 2 [SARS-CoV-2] outbreak in January 2020, many clinical studies are being carried out with the aim of combating or eradicating the disease altogether. However, so far, developing coronavirus disease 2019 (COVID-19) detection kits or vaccines has remained elusive. In this regard, the development of antiviral nanomaterials by surface engineering with enhanced specificity might prove valuable to combat this novel virus. Quantum dots (QDs) are multifaceted agents with the ability to fight against/inhibit the activity of COVID-19 virus. This article exclusively discusses the potential role of QDs as biosensors and antiviral agents for attenuation of viral infection.

KEYWORDS

antivirals, influenza pandemic, nanomaterials, quantum dots, SARS-CoV-2

1 | INTRODUCTION

COVID-19 (coronavirus disease 2019) is a highly pathogenic viral pneumonia–like infection that has now become a great pandemic. According to the World Health Organization (WHO), globally, the virus has infected 5,204,508 people; importantly, 337,687 (6.5%) of the infected individuals had died. The WHO has so far classified the cases primarily based on the transmission that occurred through community transmission, case clusters, and sporadic cases.[1] The total number of cases reported in America and Europe has increased tremendously in recent times. Concurrently, regions like Eastern, Western Pacific, South-East Asia, and Africa are showing similar trends, although with a less mortality rate. The underlying rationale behind this difference is attributed to the adaptiveness of COVID-19. In accordance with the data available so far, it has been reported that infected people will experience mild to severe acute respiratory tract infections.[2] People with underlying medical problems (e.g. cardiovascular disease, cancer, and diabetes) or those aged 60 years or older are more prone to develop a high risk of serious illness (WHO Situation Report–1).[3] Hitherto, several recommendations have been made to limit exposure, such as by maintaining personal hygiene and social distancing.

2 | BIOLOGY OF COVID-19

The WHO characterizes COVID-19 as a pandemic disease. The disease is caused by the virus of the genus *Betacoronavirus* which has likely originated from bats. The virus causes severe respiratory disease in humans.[4] COVID-19 shows a sequence similarity index of 79% and 50% with SAR-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV), respectively.[5] The structure of COVID-19 consists of a single-stranded positive-sense RNA with about 30,000 nucleotides. Besides, COVID-19 possesses five structural proteins, namely, (i) the spike (S), (ii) nucleocapsid, (iii) envelope, (iv) membrane, and (v) hemagglutinin esterase dimer proteins (Figure 1).[6] Predominantly, the S protein (spike protein) plays a vital role in infecting cells by determining the host antibodies and neutralizing them.[7] Moreover, the S protein has a stronger affinity toward the

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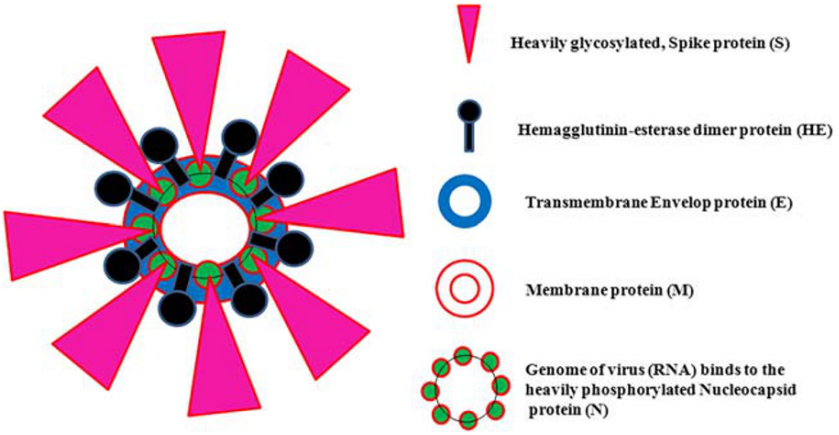

FIGURE 1 Structure of COVID-19. COVID-19, coronavirus disease 2019

human receptor ACE2 (angiotensin-converting enzyme 2) upon entering the host cells.[8] ACE2 is an enzyme attached to the cell membranes of the lower respiratory tract of lungs, stomach, small intestines, colon, kidney, lymph nodes, and liver bile ducts.[9] As a result, ACE2 is considered a major entry point of COVID-19 (Figure 2).

3 | COVID-19 DIAGNOSIS

Extensive research is being carried out worldwide to develop drugs targeting COVID-19.[10] To date, however, no therapeutics or vaccines have been approved by the United States Food and Drug Administration agency for treating patients with COVID-19. Therefore, at this point, early diagnosis of COVID-19 plays a pivotal role in identifying and quarantining a person infected with COVID-19 to prevent further spread of the virus. In this regard, several surveillance monitoring systems have been developed to curb the spread of COVID-19. Besides, diagnostic methodologies, including nucleic acid–based testing (reverse transcriptase–polymerase chain reaction), computed tomography scans, and X-rays, are used to adumbrate COVID-19.[6] Among these, the nucleic acid–based

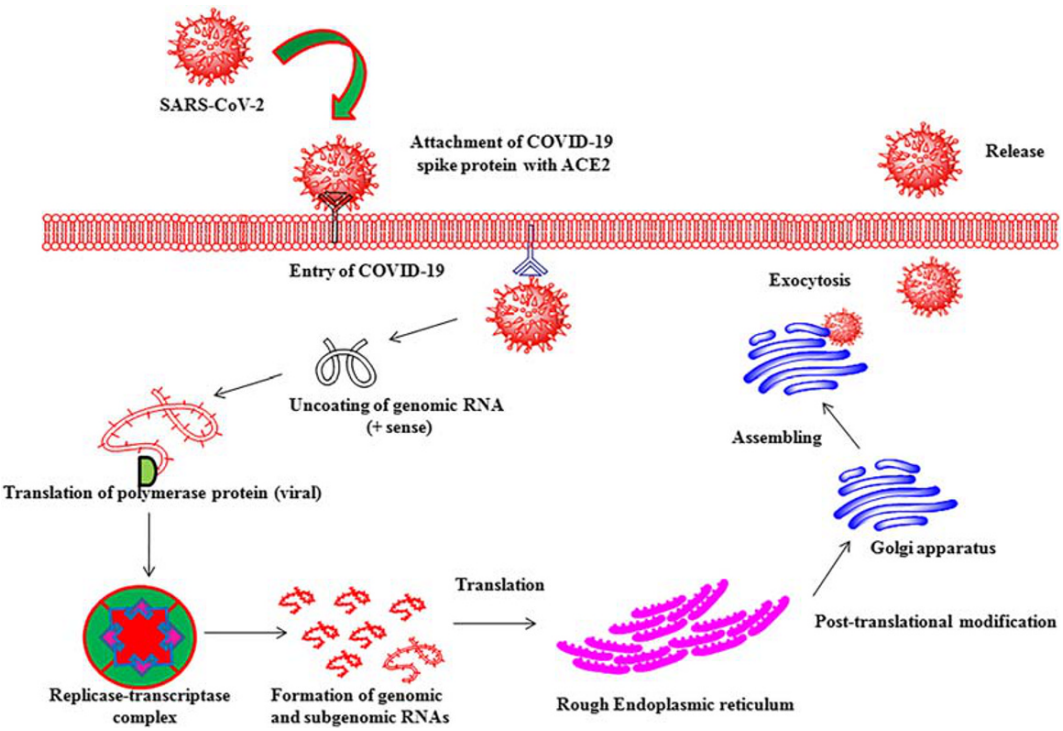

FIGURE 2 Entry mechanism of COVID-19. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV, severe acute respiratory syndrome coronavirus

testing of COVID-19 appears promising. However, the host response to such testing needs further investigation. Currently, most diagnostic aids are at the proof-of-concept state.

4 | THERAPEUTICS AVAILABLE FOR COVID-19

At present, supportive medication based on symptomatic conditions is administered as the first-line treatment for individuals with likely infection. Moreover, therapeutic options such as antiviral therapy, antibiotics, corticosteroids, and re-purposed and anti-inflammatory medications are being evaluated in clinical trials.[11] However, the precise drug or a combination of drugs required to fight COVID-19 remains unclear. As a result, for the time being, antiviral therapy–based medications such as remdesivir, lopinavir–ritonavir, and favipiravir are used as prodrugs to inhibit the activity of the viral RNA polymerase.[12] Likewise, drugs such as chloroquine and its derivative hydroxychloroquine exhibit antiviral (against severe acute respiratory syndrome coronavirus [SARS-CoV] and human coronavirus OC43 [HCoV-OC43]) and prophylactic activities, respectively.[13–15] Preliminary research findings suggest that chloroquine and its derivative hydroxychloroquine can be used to treat COVID-19, as it has the ability to interfere with viral–cell effusion.[16] In general, a few anti-inflammatory drugs such as glucocorticoids, tocilizumab, and siltuximab are used for treating COVID-19. However, the side effects that arise from these medications are not known in detail. In some cases, convalescent plasma therapy is also performed in which immunoglobulins were retrieved from patients who recovered from COVID-19 to develop an enhanced humoral response.

5 | QUANTUM DOTS FIGHT COVID-19

The application of nanomaterials in the field of nanobiotechnology is revolutionizing medical approaches used for the diagnosis and treatment of therapeutic diseases. In recent years, these nanomaterials have been used to selectively release the drug to the damaged cells or tissues in cancer treatment. The role of nanomaterials can also be extended to viral infectious diseases such as the human immunodeficiency virus (HIV), ebolavirus, and SARS-CoV.[17] Nanomaterials have a high surface-to-volume ratio which allows them to bind to several ligands on the host cells and makes them resistant to the viral attachment by multivalent interaction.

"Quantum dots (QDs)," which are also called "semiconductor nanomaterials," conjugate with high fluorescent probes, which are crucial for the detection and long-term fluorescence imaging of various cellular processes.[18,19] Compared with tunable plasmonic nanoparticles (10–300 nm), the size of the QDs ranges from 1 to 10 nm with tunable optical wavelength. Therefore, QDs have been identified as a novel fluorescent probe for molecular imaging.[20] Because of these exceptional properties, QDs can be considered a remarkable agent to fight against viral infections. Moreover, the incorporation of potential biocompatible carriers can aid in interdisciplinary research and allow clinical approaches in combating the virus. In this minireview, we discuss the role of QDs as carriers/labeling drugs or drug carriers (Figure 3).

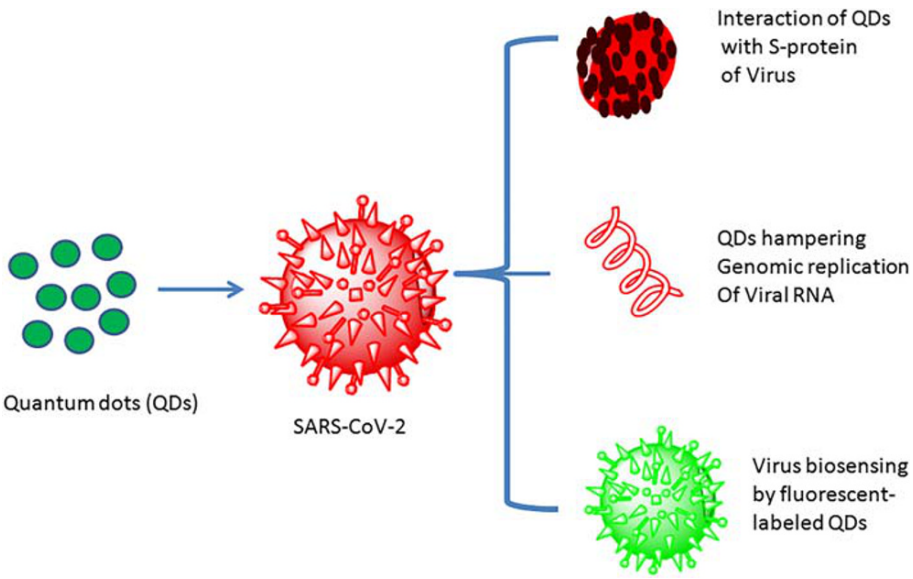

FIGURE 3 Schematic representation of the actions exerted by QDs on SARS-CoV-2. QD, quantum dot; S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2

6 | MODE OF ACTIONS OF QDS

The decisive contrivance associated with expunging SARS-CoV-2 infections by QDs could gain a substantial interest among researchers. The primary rationale for employing QDs may be ascribed to their traceability under a specific wavelength of light.[21] Besides, QDs can be tunable into the desired size (1–10 nm) and shape that effectively targets/penetrates SARS-CoV-2 with a size range between 60 and 140 nm.[22] The positive surface charge of carbon-based QDs could be used to sequester/disable the S protein of SARS-CoV-2.[23] Furthermore, cationic surface charges exhibited by QDs interact with the negative RNA strand of the virus, leading to the production of reactive oxygen species within SARS-CoV-2.[24,25] Du *et al.* demonstrated the antiviral effect of carbon dots (CDs) against pseudorabies virus and porcine reproductive and respiratory syndrome virus.[26] CDs induce the activation of interferon-stimulated genes, particularly interferon-α production, which suppresses viral replication. Further, incorporation of desired functional groups with QDs could effectively interact with entry receptors of SARS-CoV-2 and affect genomic replication.[17] Accordingly, the antiviral potential of CDs derived from 4-aminophenyl boronic acid hydrochloride (4-AB/C-dots) showed inhibitory properties against herpes simplex virus type 1, with CDs specifically acting on the early phase of viral infection.[27] Very recently, Łoczechin *et al.* demonstrated that different CDs prepared by hydrothermal carbonization and conjugation with boronic acid (carbon quantum dots-3) exert antiviral properties against the highly pathogenic human coronavirus in a dose-dependent manner.[28] Further, the functional group of CDs was found to interact with the S protein of human coronavirus-229E, and thus prevent the entry and interaction of the virus with the host cell membrane. Analogously, the benzoxazine monomer–derived CDs directly bind to the surface of virions (Japanese encephalitis, Zika, and dengue viruses, porcine parvovirus, and adenovirus-associated virus) and thus impede the virus–host cell interaction.[29] Similarly, the Gly-CDs derived from glycyrrhizic acid exerted excellent antiviral properties by suppressing the propagation of porcine reproductive and respiratory syndrome virus.[30]

In addition, the use of conventional biocompounds (e.g. curcumin) in the synthesis of QDs can offer a suitable choice of antiviral agents.[31] Although the aforesaid studies demonstrated the broad spectrum of antiviral activity exhibited by different CDs, their precise mode of action remains unclear. A significant limitation of QDs as an antiviral agent is their *in vivo* toxicity. Keep this in mind, optimization of QDs and further detailed experimental approaches with novel functional molecules against SARS-CoV-2 would extrapolate nanostructures for COVID-19 therapeutics to annihilate the life-threatening disease in immediate future.

7 | QDS AS VIRUS BIOSENSORS

One of the exciting approaches is to study the structure and life cycle of microorganisms (bacteria, fungi, and viruses) *in vivo* through fluorescence imaging. Besides the recently developed antimicrobial nanomaterials, graphene QDs and carbon QDs, show increased application for the biosensing of microbes, and thus can be used as an alternative medical diagnosis method.[17,32] In 2008, the use of QDs for labeling the envelope of virus has been demonstrated followed by the investigation of the uptake mechanism.[33]

Carbon QDs are now predominant imaging probes (chemosensors and biosensors) for sensing microbes/biomolecules. It has been demonstrated that the carbon QDs in combination with ultrasensitive lateral flow immunoassay system could efficiently sense the influenza A virus subtypes with high specificity compared with traditional testing methods.[32] Similarly, biosensing of the infectious bronchitis virus was achieved by chiral zirconium QDs with blue fluorescence emission.[34] Ashiba *et al.* developed QD fluorescent labels to increase the sensitivity of surface plasmon resonance–assisted fluoroimmunoassay, which efficiently sensed the norovirus virus–like particles.[35] Further, QDs in combination with transcription activator–like effectors have been used for live-cell imaging to identify the single-gene loci of HIV-1 in human chromosomes.[36] Liu *et al.* reported that CDs prepared from the powdered form of young barley leaves exhibit different fluorescent colors such as blue (b-CDs) and cyanin (c-CDs), which have been utilized for selective cell imaging. The b-CDs can selectively enter the cytoplasm of PK-15 cells, whereas the c-CDs dispersed over the entire cell and also in the nucleus.[37] Besides, the b-CDs displayed antiviral activity against pseudorabies virus. In the current scenario, the COVID-19 infection is rapidly spreading, and the onset of symptoms varies between individuals. Therefore, there is an urgent need to identify new diagnostic methods. In this regard, identifying or synthesizing novel fluorescent-based QDs or customizing any of the aforesaid QDs may assist researchers in developing efficient diagnostic method(s) for COVID-19.[38]

8 | FUTURE PREDICTIONS AND CONCLUSION

Resistance to antiviral drugs and the emergence of mutant virus strain are the significant implications in

conventional therapeutic strategies. The ultimate challenge is the prevention of COVID-19 spreading and exterminating viral infection from the human community. In the present scenario, the increasing incidence of COVID-19 cases is pressurizing scientists to develop vaccines based on clinical trials. Hitherto, no specific vaccines are available for COVID-19 treatment, but many ongoing clinical trials are evaluating potential therapeutics. Therefore, the exploration of a novel antiviral agent, which targets the viral entry and its interaction with the host, would potentially attenuate the viral infection. Based on the initial findings, drugs such as chloroquine, hydroxychloroquine, ritonavir, lopinavir have responded well against COVID-19. However, the development of precise molecules to fight against COVID-19 is the utmost priority. A detailed investigation about the uptake and targeted delivery of chloroquine and its derivatives by QDs would certainly provide insights and reveal the molecular mechanism of hydroxychloroquine-induced modulation of the COVID-19 life cycle. The use of QDs against COVID-19 is also a better choice because of its enormous therapeutic efficacy. Besides, QDs can be considered as a powerful imaging probe in diagnostics and prognostics. Furthermore, therapeutic molecules may be functionalized or coated onto the surface of QDs to increase the drug release profile, subsequently targeting COVID-19. However, caution should be exercised to avoid renal filtration and other side effects.

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CONFLICTS OF INTEREST

None declared.

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REFERENCES

[1] S. T. Al Awaidy, A. A. Al Maqbali, I. Omer, S. Al Mukhaini, M. A. Al Risi, M. S. Al Maqbali, A. Al Reesi, M. Al Busaidi, F. H. Al Hashmi, T. K. Al Maqbali, V. Vaidya, E. S. A. Al Risi, T. K. Al Maqbali, A. A. Rashid, M. A. H. Al Beloshi, A. Etemadi, F. Khamis, *J Infect Public Health* **2020**, *13*, 679. https://doi.org/10.1016/j.jiph.2020.03.002

[2] K. Y. Ho, K. S. Singh, A. G. Habib, B. K. Ong, T. K. Lim, E. E. Ooi, B. K. Sil, A.-E. Ling, X. L. Bai, P. A. Tambyah, *J Infect Dis* **2004**, *189*, 642. https://doi.org/10.1086/381558

[3] K. Liu, Y. Chen, R. Lin, K. Han, *J Infect* **2020**, *80*, e14. https://doi.org/10.1016/j.jinf.2020.03.005

[4] H. Li, S.-M. Liu, X.-H. Yu, S.-L. Tang, C.-K. Tang, *Int. J. Antimicrob. Agents* **2020**, *55*, 105951. https://doi.org/10.1016/j.ijantimicag.2020.105951

[5] Scientific research progress of COVID-19/SARS-CoV-2 in the first five months - Li - - Journal of Cellular and Molecular Medicine - Wiley Online Library, (n.d.). https://onlinelibrary.wiley.com/doi/10.1111/jcmm.15364 (accessed May 25, 2020).

[6] B. Udugama, P. Kadhiresan, H.N. Kozlowski, A. Malekjahani, M. Osborne, V.Y.C. Li, H. Chen, S. Mubareka, J.B. Gubbay, W. C.W. Chan, Diagnosing COVID-19: The Disease and Tools for Detection, ACS Nano. (**2020**). https://doi.org/10.1021/acsnano.0c02624, 14, 3822.

[7] S. Rosales-Mendoza, V. A. Márquez-Escobar, O. González-Ortega, R. Nieto-Gómez, J. I. Arévalo-Villalobos, *Vaccine* **2020**, *8*, 183. https://doi.org/10.3390/vaccines8020183

[8] S. Jiang, C. Hillyer, L. Du, *Trends Immunol.* **2020**, *41*, 355. https://doi.org/10.1016/j.it.2020.03.007

[9] T. Magrone, M. Magrone, E. Jirillo, Focus on Receptors for Coronaviruses with Special Reference to Angiotensin-converting Enzyme 2 as a Potential Drug Target - A Perspective, Endocr Metab Immune Disord Drug Targets. (**2020**). https://doi.org/10.2174/1871530320666200427112902, 20.

[10] M. A. Chary, A. F. Barbuto, S. Izadmehr, B. D. Hayes, M. M. Burns, *J Med Toxicol* **2020**, 1. https://doi.org/10.1007/s13181-020-00777-5

[11] Q. Zhang, Y. Wang, C. Qi, L. Shen, J. Li, *J Med Virol* **2020**, *92*, 540. https://doi.org/10.1002/jmv.25733

[12] S. Ş Yavuz, S. Ünal, *Turk J Med Sci* **2020**, *50*, 611. https://doi.org/10.3906/sag-2004-145

[13] E. Haładyj, M. Sikora, A. Felis-Giemza, M. Olesińska, *Reumatologia* **2018**, *56*, 164. https://doi.org/10.5114/reum.2018.76904

[14] M. J. Vincent, E. Bergeron, S. Benjannet, B. R. Erickson, P. E. Rollin, T. G. Ksiazek, N. G. Seidah, S. T. Nichol, *Virol J* **2005**, *2*, 69. https://doi.org/10.1186/1743-422X-2-69

[15] E. Keyaerts, S. Li, L. Vijgen, E. Rysman, J. Verbeeck, M. V. Ranst, P. Maes, *Antimicrob. Agents Chemother.* **2009**, *53*, 3416. https://doi.org/10.1128/AAC.01509-08

[16] B. Russell, C. Moss, G. George, A. Santaolalla, A. Cope, S. Papa, M. Van Hemelrijck, *Ecancermedicalscience* **2020**, *14*. https://doi.org/10.3332/ecancer.2020.1022

[17] D. Iannazzo, A. Pistone, S. Ferro, L. De Luca, A. M. Monforte, R. Romeo, M. R. Buemi, C. Pannecouque, *Bioconjugate Chem.* **2018**, *29*, 3084. https://doi.org/10.1021/acs.bioconjchem.8b00448

[18] M. Boles, D. Ling, T. Hyeon, D. Talapin, *Nat. Mater.* **2016**, *15*, 141. https://doi.org/10.1038/nmat4526

[19] S. R. Mudshinge, A. B. Deore, S. Patil, C. M. Bhalgat, *Saudi Pharmaceutical Journal* **2011**, *19*, 129. https://doi.org/10.1016/j.jsps.2011.04.001

[20] D. Peer, J. M. Karp, S. Hong, O. C. Farokhzad, R. Margalit, R. Langer, *Nat. Nanotechnol.* **2007**, *2*, 751. https://doi.org/10.1038/nnano.2007.387

[21] S. Jha, P. Mathur, S. Ramteke, N. K. Jain, *Artificial Cells, Nanomedicine, and Biotechnology* **2018**, *46*, 57. https://doi.org/10.1080/21691401.2017.1411932

[22] M. Prajapat, P. Sarma, N. Shekhar, P. Avti, S. Sinha, H. Kaur, S. Kumar, A. Bhattacharyya, H. Kumar, S. Bansal, B. Medhi,

Indian J Pharm **2020**, *52*, 56. https://doi.org/10.4103/ijpIJP_115_20

[23] D. Ting, N. Dong, L. Fang, J. Lu, J. Bi, S. Xiao, H. Han, *ACS Appl Nano Mater* **2018**, *1*, 5451. https://doi.org/10.1021/acsanm.8b00779

[24] X. Dong, M. M. Moyer, F. Yang, Y.-P. Sun, L. Yang, *Sci. Rep.* **2017**, *7*, 519. https://doi.org/10.1038/s41598-017-00675-x

[25] L. Chen, J. Liang, *Korean J Couns Psychother* **2020**, *112*, 110924. https://doi.org/10.1016/j.msec.2020.110924

[26] T. Du, J. Liang, N. Dong, L. Liu, L. Fang, S. Xiao, H. Han, *Carbon* **2016**, *110*, 278. https://doi.org/10.1016/j.carbon.2016.09.032

[27] A. Barras, Q. Pagneux, F. Sane, Q. Wang, R. Boukherroub, D. Hober, S. Szunerits, *ACS Appl. Mater. Interfaces* **2016**, *8*, 9004. https://doi.org/10.1021/acsami.6b01681

[28] A. Łoczechin, K. Séron, A. Barras, E. Giovanelli, S. Belouzard, Y.-T. Chen, N. Metzler-Nolte, R. Boukherroub, J. Dubuisson, S. Szunerits, *ACS Appl. Mater. Interfaces* **2019**, *11*, 42964. https://doi.org/10.1021/acsami.9b15032

[29] S.-L. Huang, *Adv. Drug Delivery Rev.* **2008**, *60*, 1167. https://doi.org/10.1016/j.addr.2008.03.003

[30] T. Tong, H. Hu, J. Zhou, S. Deng, X. Zhang, W. Tang, L. Fang, S. Xiao, J. Liang, *Small* **2020**, *16*(13), 1906206. https://doi.org/10.1002/smll.201906206

[31] F. Lin, Y.-W. Bao, F.-G. Wu, *C — Journal of Carbon Research* **2019**, *5*, 33. https://doi.org/10.3390/c5020033

[32] F. Wu, M. Mao, Q. Liu, L. Shi, Y. Cen, Z. Qin, L. Ma, Ultra Sensitive Detection of Influenza A Virus Based on Cdse/Zns Quantum Dots Immunoassay, SOJ Biochemistry. 2 (**2016**). https://symbiosisonlinepublishing.com/biochemistry/biochemistry19.php (accessed May 26, 2020).

[33] K.-I. Joo, Y. Lei, C.-L. Lee, J. Lo, J. Xie, S. F. Hamm-Alvarez, P. Wang, *ACS Nano* **2008**, *2*, 1553. https://doi.org/10.1021/nn8002136

[34] H. Ahamed, J. Mohamed, K. Arunachalam, D. Raiyaan, M. S. Musthafa, S. S. Begum, H. Van Doan, *Aquaculture Reports* **2020**, *17*, 100341.

[35] H. Ashiba, Y. Sugiyama, X. Wang, H. Shirato, K. Higo-Moriguchi, K. Taniguchi, Y. Ohki, M. Fujimaki, *Biosens. Bioelectron.* **2017**, *93*, 260. https://doi.org/10.1016/j.bios.2016.08.099

[36] Y. Ma, M. Wang, W. Li, Z. Zhang, X. Zhang, T. Tan, X.-E. Zhang, Z. Cui, *Nat. Commun.* **2017**, *8*, 1. https://doi.org/10.1038/ncomms15318

[37] H. Liu, Y. Bai, Y. Zhou, C. Feng, L. Liu, L. Fang, J. Liang, S. Xiao, *RSC Adv.* **2017**, *7*, 28016. https://doi.org/10.1039/C7RA03167J

[38] S.-L. Liu, Z.-G. Wang, H.-Y. Xie, A.-A. Liu, D. C. Lamb, D.-W. Pang, *Chem. Rev.* **2020**, *120*, 1936. https://doi.org/10.1021/acs.chemrev.9b00692

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