Invited Review Article

Is Nanoscience the Way Forward to COVID-19 Like Diseases?

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Dr. Kalarical Janardhanan Sreeram, a fellow of the Royal Society of Chemistry, UK and Society of Leather Technologists and Chemists, UK is the Director of the CSIR - Central Leather Research Institute since December 2019. Prior to this, he was the head of the testing facilities of the institute, where his contributions towards development of test methods for leather and allied products and achieving the ISO 17025:2017 standards were highly acclaimed.

Dr. Sreeram has made important contributions to the Green Chemistry of Chromium that has opened up new paths for better industrial management of this metal ion at the global level. These contributions have led to his becoming the first researcher with a degree in leather technology from Anna University to receive the CSIR Young Scientist Award in 2004.

Dr. Sreeram has also contributed immensely to the development of environmentally benign and cool pigments from rare earth metal ions, as a replacement to the pigments based on toxic metal ions such as chromium, lead, mercury etc. He is also credited with commercially successful technologies for the avoidance of formaldehyde in tanning agents. During the last five years, in order to exploit the advantages of nanoscience for developing materials with unique applications, Dr. Sreeram has developed a range of functionalized metal and metal oxide nanoparticles with potential applications in crosslinking of proteins, a work which led his being recognized by the International Union of Leather Technologists and Chemists Societies, with the International Union of Research Award.

Dr. Sreeram has an impressive publication record, with 95 papers in national and international journals, 1566 citations and h-index of 20. He also has 19 patents filed to his credit, with several technology transfers/consultancy activities. The success of Dr. Sreeram's contributions stems from his fundamental understanding of the chemistry of metal ions with which he has worked.

Dr. Sreeram has also been involved in science communication, specifically in the area of sustainable manufacturing. He is honorary faculty of the Anna University and has guided 6 students for their doctoral dissertation in chemistry at the University of Madras/ Anna University. The ability to lead teams for achieving high goals is his strength.

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Abstract

The outbreak of COVID-19 in late 2019 has led to a rush for specific treatment protocols, vaccines and medical devices. Little did scientists realize that the science that they pursued, with outputs in the form of patents and publications, was now required to be delivered on the field. This article reviews the information available in open source on this disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the potential for nanomedicine in the treatment and development of medical devices for handling such conditions.

Key words : COVID-19, SARS-CoV-2, nanomedicine, Coronavirus diagnosis, Personnel Protective Equipment, Theranostics with Nanoparticles

Introduction

An epidemic outbreak in Hubei, China led the researchers to use Next-Generation sequencing of nucleic acids from the patient samples. A novel strain of coronavirus (CoV) was identified as the causative agent. Subsequent protocols such as isolation and *in vitro* culturing led to the designation of this virus as SARS-CoV-2 and the disease as Covid-19 by World Health Organization. The corona virus belongs to the *Coronaviridae* family and consists of the α, β, γ, and δ genera, with α, β CoV causing human infections. The SARS belongs to the β-genera, subgenus *sarbecovirus* and subfamily *Orthocoronavirinae*.[1] There is very little information on the viral origin, epidemiology and treatment of Covid-19. Based on the information generated about the Covid-19 patients, the high-risk groups are people with low or compromised immunity, other diseases like cancer, diabetes etc., and elderly.

Coronavirus and its Transmission

The scanty information from the microscopic evaluation of the virus indicates a spherical morphology carrying surface projects of spike proteins and size in the range of 60-140 nm.[2] The Genome length has been predicted at about 26-32 kb. Within a short time scientists have sequenced and publicly made available the complete genome of Covid-19, which is said to be a single-strand (+) RNA genome of 30 kb length,[3] with 70% of the genome being non-structural proteins like cysteine protease, main protease and RNA polymerase.

Aerosol transmission and direct contact have been considered as possible routes for the transmission of Covid-19. Thus, when a carrier coughs, sneezes or even laughs, droplets (> 5 microns) and aerosols (< 5 microns) are generated. While droplets would settle down by gravity easily, aerosols can travel through air for a longer time and subsequently enter the respiratory track of nearby individuals or contaminate surfaces.[4] There are earlier reports that SARS-CoV can travel more than six feet and hand contact with surfaces contaminated with the virus can lead to pathogen transfer to eyes, nose or mouth, thus transmitting the disease.[5,6] The possibility of a fecal-oral transmission of SARS-Cov-2 is also not being ruled out, especially in areas with poor sanitation, handling of stools of patients, sewage from hospitals etc.[7] Further, research on Human coronavirus indicates that the virus can remain infectious on inanimate surfaces for up to 9 days. The SARS-CoV had a persistence for 4 – 5 days on metal, ceramic, glass, plastic, and PVC surfaces.[8]

Diagnosis Protocols

Covid-19 diagnosis predominantly relies on real-time reverse transcription polymerase chain reactions (RT-PCR) of nucleic acid.[9] The Hologic Panther Fusion system consists of fully automated process consisting of RNA extraction, amplification of target sequences and real time PCR detection.[10] Chest computed tomography has also been reported for disease diagnosis with added advantage of evaluating therapeutic efficacy.[11] RNA-guided CRISPR or Cas nuclease-based nucleic acid detection is one of the next generation diagnostic technologies with high sensitivity, specificity and reliability and having potential application in SARS-CoV diagnosis.[12] The challenge, however, in a pandemic situation is to convert these or other technologies into point-of-care technologies that are cheap and provides reliable screening data in a fast manner. A paper strip-based testing assay that can within an hour detect the viral RNA of the novel coronavirus SARS-CoV-2 is under development at CSIR-IGIB.

Personnel Protective Equipment

Being a virus transmitted through close contact and aerosols, prevention and mitigation involves significantly the use of personnel protective equipment. Wearing a medical mask by those having respiratory symptoms and use of PPE described by WHO under its infection prevention and control of pandemic infections is essential for those caring patients with COVID-19.[13] One of the significant issues with the PPE is the ability of the virus to remain persistent on inanimate surfaces. This poses challenges of disposal of the PPE. The challenge is exemplified by the absence of protocols for reuse in the case of many of the PPEs, more so in the case of face masks.

Therapeutic Possibilities for Covid-19

In the initial phase of Covid-19, the focus was on provision for supportive care such as ventilation and fluid management. Subsequently, doctors in various countries have resorted to using anti-virals, anti-malarials or a combination of these as treatment with varying levels of success. Among the anti-viral agents, oseltamivir, ganciclovir, lopinavir/ritonavir and remdesivir are being tried out.[14] Chloroquine phosphate is the most popular anti-malarial drug that is being used for Covid-19 treatment.[15]

Many herbal compounds used in traditional Chinese medicine are now being screened as anti-SARS-CoV therapy. The use of molecular docking studies and other simulation techniques have aided the screening of potential therapeutics. For this, the binding database has been selected from the genome sequence and the ability of the drug molecule to dock in the catalytic pockets near the active sites of RdRp. The RdRp has an active site in the form of a deep groove for the polymerization of RNA and is considered as a potential therapeutic target. Theaflavin, a polyphenolic compound in black tea, was able to dock in the catalytic pocket near RdRp, and thus could possibly block the active site in the groove of RdRp.[16]

Passive immunization with convalescent plasma has also been reported to improve oxygenation and reduce inflammation and viral load.[17]

Theranostics with Nanoparticles

Let us now recap some of the features of the COVID-19 and the methodologies employed till date in diagnosis, treatment and protection of patient care personnel.

a. The Genome sequence and thus the active site to target in the virus is known

b. The virus is persistent on most of the inanimate surfaces, thus contact transmission is of high order

c. Diagnosis tools currently employed are time consuming and point of care diagnosis tools are the need of the hour

d. Drug repurposing and targeted delivery are the way forward as it shortens the concept to use time period.[18]

Antiviral Nanoparticles

Researchers have developed a library of polymeric nanoparticles that can bind and neutralize toxins such as Staphylococcus aureus.[19] Traditional medicine details a large number of plant extracts being employed as antivirals. Ben-Shabatet al., in a review article on the antiviral effect of phytochemicals, indicated that a large number of them were ethanolic extracts with effectivity towards HIV, human rotaviruses etc.[20] Liposomes, nanoparticles, nanoemulsions, nanosuspensions etc., have been reported for enhancing the aqueous solubility and oral absorption, systemic bioavailability, and better activity.

Carbohydrate coated gold nanoparticles loaded with anti-HIV prodrugs such as abacavir and lamivudine have been developed with pH sensitive release pattern.[21] Nanostructured lipidic carriers of lopinavir have been reported to have 2.8-fold improvement over plain lopinavir in brain biodistribution potential.[22] It needs to be recalled that lopinavir has been repurposed as a powerful inhibitor of coronavirus proteinase.[23] Graphene oxide sheets with silver nanoparticles have themselves been reported to have antiviral activity against feline coronavirus.[24] Fe_3O_4 coated with oleate and carrying oseltamivir was reported to bind to DNA groove much efficiently than oseltamivir.[25]

Nanovectors or Potential Vaccine Candidates

Current vaccines have limitations of production capacities, administration schedules, storage needs and cost. A promising methodology is the use of messenger RNA that encodes the main virus antigen. While the mRNA vaccines are safe, the immune response depended on the mode of administration. Lipid nanoparticles have been reported as encapsulants for the mRNA.[26] ZnO nanocomposites have also shown promise as vaccine adjuvant.[27]

Nanoparticles in Virus Detection

Cell culture coupled with electron microscope has been in use for virus isolation and detection since 1950. During the 1980s, immunoassays and polymerase chain reaction (PCR) boosted diagnostic virology. In recent years serological and molecular detection techniques have become standard methods for virus detection.[28] The molecular detection techniques consisting of polymerase chain reaction, dot hybridization, gene chips, nucleic acid sequence-based amplification and loop mediated isothermal amplification have been influenced by the advent of nanotechnology. The first instance of human papillomavirus detection by gold nanoparticles was reported in 1997.[29] Self-assembled chiroplasmonic gold nanoparticles have also been reported as ultrasensitive immunosensors for coronavirus in blood samples.[30] However, the use of nanoparticles in virus detection is limited by the properties of the nanoparticles themselves.

Point of care technology is today a USD 37 billion market. It typically consists of sample preparation, detection/readout and interpretation. In the sample preparation stage, magnetic nanoparticles have been reported to replace several conventional steps such as centrifugation, precipitation and filtration.[31]

Antiviral Coating on Protective Equipment

Mixtures of silver nitrate and titanium dioxide nanoparticles have been reported as coatings on hospital facemask during clinical procedures as protectants against infectious agents.[32] Pegylated nanoparticles, such as that of ZnO have been reported with increased antiviral activity.[33] The use of such nanoparticles as an antiviral finishing treatment as against the current practices of mere antibacterial coatings would be advantageous in the present circumstances of handling COVID-19 type of viruses.

The Way Forward

There is a significant scope for nanoparticles to enable management of viruses such as COVID-19. Nanoparticles could enable drug repurposing, targeted delivery and reduction in side effects, enable point of care diagnosis development and also reduce contact-based transmission of disease by protecting the surfaces. However, the translation of nano research from lab to market has not been significantly forthcoming. The technology readiness levels of intellectual properties related to nanoparticles in such applications have been low, predominantly due to size and shape dependent property changes associated with the nanoparticles. There is a need to develop robust engineering methods for upscaling the production of nanoparticles or nanocomposites. Technology maturity in terms of a) reproducibility (kilograms or tons/day), b) nanoparticle production facilities (kilograms or tons/batch or continuous processes), c) scale-up investment, and d) safety and associated end-of-pipe treatment systems on full rate production are to be in place as fast as possible for nanoscience to be the way forward for management of COVID-19 like diseases.

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