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EDITORIAL

Manipulative magnetic nanomedicine: the future of COVID-19 pandemic/endemic therapy

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1. Introduction: COVID-19 pandemic or endemic as health emergency

Since the Spanish flu outbreak (1918), many pandemics and/or endemics related to a viral infection such as H1N1, H5N1, human immunodeficiency virus (HIV), Ebola, Zika, and coronavirus have surprised mankind time-to-time due to their sudden appearance, severe adverse health effect, loss of lives, socio-economic burden, and a damaged economy. Such deadly infectious viruses originated from natural reservoirs and then infect humans via spillover mechanism. During infection progression, viruses affect the human biological system and become a part of the host genome and then make structural changes in its structure to survive or infect longer. These infections can cause permanent disorders, may be death, if a patient is immunocompromised and could not fight against virus life-cycle associated pathways and viral infection progression.

One such pandemic and/or endemic is the recent COVID-19 infection associated with new server acute respiratory syndrome coronavirus (SARS-CoV-2), investigated by Chinese clinicians in Dec 2019. Chinese health agencies noticed a rapid increment in seasonal flu cases, and this emerged as a very serious health issue due to the ineffectiveness of prescribed therapies [1,2]. Systematic investigations conducted on this infectious disease by experts confirmed and claimed that SARS-CoV-2 virus infection is dramatically affecting the respiratory system of every age patient via affecting their lung function. Although SARS-CoV-2 virus protein exhibited 70% to 80% genomic profile like SARS-CoV-1 (2002 outbreak) and middle east respiratory syndrome (2012 outbreak), but its viral infection mechanism, pathogenesis, mortality per cent, and other risks are different, unknown, and serious than SARS and MERS [2]. Considering the severity of COVID-19 infection and variation in SARS-CoV-2 virus strains, this outbreak was first declared as an international health emergency; then, a pandemic due to global spread [2], and now experts are projecting this as an endemic due to post-infection effects and possibilities of reoccurrence like HIV [3]. This infection is emerging very challenging due to 1) human-to-human transmission via aerosolization, 2) ability to affect lung rapidly because of easy binding between Spike (S1) protein of SARS-COV-2 virus and host cell membrane receptors like angiotensin-converting enzyme 2 (ACE-2) and TMPRSS-2 protein, this makes virus replication easy [4].

A successful COVID-19 infection management is not the only issue to deal with the respiratory system as it affects lung function. But the SARS-CoV-2 virus infection also severely affects other important body organs including the heart, liver, eye, gut, and brain as well. This is the reason that recovery of a COVID-19 infected patient is slow and sometimes the patient exhibits permanent disorder in biological function due to weak organs and organ function [2]. Such scenarios have been investigated in asymptomatic patients as well. Keeping complete COVID-19 outbreak into consideration, health agencies were focused on 1) preparation and execution of safety guidelines, 2) exploring virus structure, genomic profiles, variability, and generate bioinformatics to understand pathogenesis, 3) developing rapid diagnostic kits, 4) optimizing available therapies, alone or in combination, 5) exploring methodologies to prevent SARS-CoV-2 transmission, 6) exploring novel therapeutics, 7) exploring aspects of therapeutic delivery at disease location, and 8) exploring combinational aspects of nanobiotechnology to support rapid testing, trapping of SARS-CoV-2, and delivery of therapeutics for not only to eradicate SARS-CoV-2 but provide long-term immunity for COVID-19 infected patient [4–6].

Based on the outcomes of big data analytics based on artificial intelligence (AI), it is suggested that recognition and eradication of the SARS-CoV-2 virus may be a time-taking procedure. Thus, all the focus is toward rapid infection diagnostics and viral infection management using state-of-the-art technologies, for example, 1) promoting physical distance and using of a mask to avoid virus transmission, 2) developing AI and internet-of-medical-things (IoMT) based strategies for rapid testing, tracking of patients, big data analytics, bioinformatics generation, developing a novel sensor for early-stage SARS-CoV-2 detection [2,5,7], and novel therapeutics and successful delivery using nanobiotechnology approach [8], the main focus of this editorial.

2. Manipulative magnetic nanomedicine: the future of COVID-19 therapy

Nanobiotechnology is emerging very promising to investigate novel methodologies for managing COVID-19 pandemic/endemic successfully [2,5]. In this direction, experts

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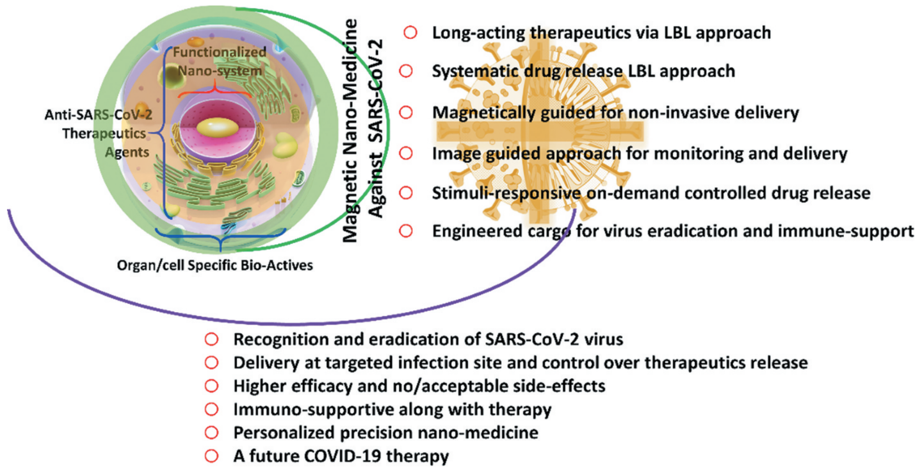

Figure 1. Systematic illustration of manipulative nanomedicine projected as future COVID-19 pandemic/endemic therapy.

have explored the opto-electro-magnetic nanosystem to detect the SARS-CoV-2 virus using a biosensing approach. Such optical, electrical, or magnetic biosensors function based on geno-sensing and immune-sensing has detected the SARS-CoV-2 virus selectively at a very low level [7,8]. These efficient-miniaturized biosensors can be operated using a smartphone and promoted for clinical application for early-stage diagnostics of COVID-19 infection. The successful integration of these SARS-CoV-2 virus sensors with AI and IoMT enables virus detection at point-of-location and sharing of bioinformatics with the medical center at the same time for timely therapeutics decision. This approach is also useful for tracking tasks and managing COVID-19 infection according to patient infection profiling. To avoid human-to-human SARS-CoV-2 virus transmission, experts have developed stimuli-responsive nanotechnology enable which can not only trap aerosol of virus size but can eradicate viruses on applying external stimulation for example nanoenable photo-sensitive virus degradation. Various types of clothes containing nanoparticles have demonstrated SARS-CoV-2 virus trapping and eradication successfully [2,9]. However, significant attention is required to increase the production and distribution of these masks for public use.

Besides, the contribution of biotech-pharma companies is also of high significance in terms of investigating novel therapeutic agents of higher efficacy with least/acceptable adverse effects. Though the SARS-CoV-2 virus is new and has exhibited strain variation which is making treatment optimization challenging. But biotechnology experts are analyzing every aspect of bioinformatics to design and develop an effective therapy based on novel anti-viral agents, CRISPR-Cas, antibodies, and vaccines[5]. Another approach to manage COVID-19 infection is to introduce or boost immunity through nutrition, for example, nutraceuticals have acted as inhibitors to prevent binding between SARS-CoV-2 virus and ACE-2 enzyme [2,8].

Investigating a therapeutic agent against the SARS-CoV-2 virus infection seems possible now but the delivery of these agents is still a remaining challenge because this virus may have numerous reservoirs over the time. It is also demonstrated that COVID-19 infection patients may temporarily or permanently have immunocompromised biological systems. Such-related adverse effects include risk of cardiac arrest, vision issues, weak respiratory system, neurological disorders (one of the serious issues because SARS-CoV-2 virus crosses the blood-brain barrier), etc. Therefore, a single therapeutic agent designed against the SARS-CoV-2 virus may not be enough to treat COVID-19 infected patients completely [1,8].

Thus, a manipulative therapy, a combination of optimized therapeutic agents, consisting of an anti-SARS-CoV-2 virus agent and immune-supportive agents will require to be optimized based on the patient infection profiling. Experts have thought about it and raised/dealing the following concerns 1) drug-to-drug interaction, 2) delivery of drug/drugs at the targeted site, 3) control over the release of drug/drugs from a therapeutic formulation, and 4) immune-supporting long-acting therapies. These tasks are challenging but needed to be managed; therefore, exploring aspects of nanomedicine could be a promising approach to develop novel therapies to manage COVID-19 infection and support the immune system along with SARS-CoV-2 virus affected organs [8].

Nanomedicine (10 to 200 nm) is a therapeutic cargo designed using an appropriate drug nanocarrier and a therapeutic agent [9–15]. Nowadays magnetic nanomedicine has performed to manage viral infection at various reservoirs even in the brain because nanomedicine is capable to cross any barriers in the body via adopting the following approaches 1) functionalization of nanomedicine with barriers specific receptors, 2) applying external stimulation like ultrasound, and 3) noninvasive guided approach like magnetically guided drug delivery system [10–12].

Besides drug delivery, magnetic nanomedicine could be formulated to deliver multiple drugs at a targeted site to achieve desired therapeutic performance due to 1) control over the release by applying external stimulation like an ac-magnetic field, 2) formulating a magnetic cargo to load multiple drugs without drug-to-drug interaction, for example, layer-by-layer (LBL) approach, and 3) the sequence of drug release can be tuned and planned according to a stage/requirement of disease condition [13–15]. The performance of such nanomedicine mainly depends on the selection of a multi-functional stimuli-response drug nanocarrier such as magneto-electric nanoparticles (MENPs) [12], opto-magnetic, opto-electromagnetic, magneto-LBL, magneto-liposome, and magneto-plasmonics nanosystem. These advanced nanomedicines not only deliver the drug/drug but also help in the recognition of drug distribution and disease progression.

Combining above mentioned salient features, manipulative magnetic nanomedicine (MMN) as one of the potential future therapy wherein control over delivery and performance if required. Such MMN has the capabilities to recognize and eradicate the SARS-CoV-2 virus to manage COVID-19 infection and symptoms. Besides, due to the flexibility of using the therapeutic agent of choice, these manipulative nanomedicines can be designed and developed as long-acting therapy for COVID-19 infection where anti-virus and immune-supportive agents can stay longer in the body without causing any side-effects. Such personalized MMN (Figure 1) is an urgently required therapy and its development should be the focus of future research with the following aims

(1) Exploring stimuli-responsive magnetic nanosystems for on-demand-controlled delivery and release.
(2) Image-guided therapy to recognize the delivery site and confirm drug release.
(3) A magnetically guided approach to delivering drugs across the barriers like the gut, BBB, etc.
(4) Magneto-LBL/liposomal approach to delivering multiple drugs to avoid drug-to-drug interaction and control over the drug release sequence. For example, an anti-virus drug should be released first then an immune-protective agent.
(5) The MMN can be customized according to patient disease profile and medical history, for example, selection of anti-SARS-CoV-2 virus agent (antibody, ARV, CRISPR-Cas, etc.,) based on patient genomic profiling.
(6) The MMN can also be customized as long-acting therapeutics that allows drug-releasing for a longer time (2–3 months), as must require therapy to manage post-COVID-19 infection effects.
(7) The MMN can be explored as personalized precision therapy.

3. Expert opinion

Based on the experiences of developing MMN to eradicate neuroHIV/AIDS, under a project of getting into the brain, using MENPs as a drug nanocarrier, magnetically guided drug delivery, and ac-magnetic field stimulation dependent controlled drug release, my team and me believes that MMN can be a future therapy against COVID-19 infection pandemic/or endemic. As it is also known that the SARS-CoV-2 virus infection is a combination of several diseases and symptoms. During the infection treatment, even after the hospital discharge, the patient may have several diseases at the same time for a longer time. Such-complicated medical conditions are not easy to deal with using conventional antiviral drugs. Thus, experts feel the demand for a new therapy that can handle multiple tasks at the same time. Keeping advancements and potentials into consideration, manipulative nanomedicine can be one of the potential COVID-19 infection therapies.

Some of the advancements in this field has been reported, for example, micro-needle-based vaccine delivery to manage COVID-19 infection. Early outcomes are exciting, but a lot must be done in terms of animal model-based trials, and followed up with FDA approval, needed prior to suggest clinical implication. To promote MNM against COVID-19 successfully, a public-private involvement-based significant research needed to be conducted in this field to create a path from a lab (in-vitro) to in-vivo (appropriate animal model) to risk assessments to clinical trials to risk assessment to human trial to risk assessment to FDA approval for public utilization. In the process of developing an anti-COVID-19 infection therapy, careful and critical safety-related risk assessments will be a crucial factor to decide progression step-by-step. This introducing AI will be a good choice to gather bioinformatics, perform big data analysis, avoid unnecessary hit-&-trial approaches, establish a relation with a biological and pathological parameter, and projection of a potential approach. Besides AI, it is also suggested to design several projects focused on every aspect of pre/post-SARS-CoV-2 virus infection, and based on assessments and analytics a potential drug nanocarrier and therapeutics agents should be selected. Developing such an approach is a multidisciplinary research approach and experts of various expertise are needed to work on the same platform to investigate MMN to combat against SARS-CoV-2 virus infection. Projecting the above mention as a necessity, this editorial is a call to experts to join hands for investigating and promoting MMN as a potential future COVID-19 pandemic/endemic therapy. I believe that the MMN approach will be in more demand as new therapeutic agents, such BNT162b2, and mRNA1273 [16], vaccine as will be investigated over the time.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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