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An open call for nano-based therapy to address COVID-19 and oncological clinical conditions

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Dear Editor,

From asymptomatic infection to pneumonia and potentially lethal consequences, there are numerous symptoms of coronavirus disease 2019 (COVID-19) illness[1]. While articles have majorly focused on the propagation, treatment and safety measures with regard to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, it is imperative to draw attention to how surgical therapies have addressed COVID-19 pandemic and how to further improve it. Numerous issues with regard to surgery have cropped up that include, reducing the operation cases, deporting personnel to a larger population infected with COVID-19, elective surgery deprogramming and a decline in the number of patients opting for surgery due to fear factors. Strong evidence permits recommending immunotherapy in COVID-19 being the first reported both horizontally and vertically acute infectious disease. Immunotherapy of COVID-19 has attained important milestones. However, major difficulties in the day-to-day clinical practice remain that need be addressed urgently. The numerous available vaccines seem to be ineffective in giving long-term protection against SARS-CoV-2 variants like omicron. Studies confirm that although the currently used vaccines induce neutralising antibodies, they are insufficiently effective. Vaccine-induced immunity seems to wane away after about 6 months after which booster doses need to be administered. Nano-based approach (nanoparticle adjuvant) could be effective in inducing protective immunity, enhanced broad-spectrum cellular and humoral immune responses, and can potentially induce long-term immunity[2].

Nanotechnology opens new vistas for strategies to prevent, diagnose and treat COVID-19 and similar viral infections. It is being employed in diagnosing and treating viral ailments and may offer a 'fresh start' addressing the toxicity, stability and bioavailability issues in the existing COVID-19 treatment strategies[3]. Nanoparticles are of miniscule size with improved solubility, surface adaptability and multifunctionality properties to help develop early diagnosis and disease prevention, better and safer personalized nanomedicines and tissue-targeted therapeutics[4]. Advances in nano-inspired antiseptics, protective equipments for healthcare personnel, nanosystems to develop diagnostics, therapeutics and preventives is a clarion call[5]. It could help counter COVID-19 by: (a) designing safer personal protective equipment for the healthcare personnel, effective antiviral molecules/compounds and surface coats; (b) designing extremely precise and responsive nanosensors to rapidly identify an infection or the immune response; (c) developing enhanced bioactive drugs that are low on toxicity, sustained release ability and better tissue targeting (e.g. to the lungs) and (d) developing more effective nano-based humoral and cellular immune response to boosting vaccines.

With the onset of COVID-19 pandemic, it was clear that dysregulated immune response against SARS-CoV-2 especially in patients with severe disease is a main pathogenesis feature, and studies to rebalance it using immune response modulators have begun. Early elimination of the virus is likely to prevent the severity of disease by limiting the immune dysregulation cascade. An important aspect is that new studies have provided vital information on antiviral therapies in COVID-19 like remdesivir and molnupiravir. As these are not immunomodulatory drugs, this compilation shall not focus on their use. This compilation intends to provide an overview of the immunotherapies targeted at various COVID-19 pathophysiology components and offer practically suitable host-directed approaches in medical practices[6]. It also discusses on the impact of COVID-19 on surgery due to the emergence as global spread of SARS-CoV-2 leading to pandemic and its effective delivery strategies.

The nascent field of immuno-oncology is at the forefront in oncotherapy. Such therapy silently elicits the immune response undeterred and activates the immune system of the body for better targeting with reduced or nil side-effects while fighting cancer, in contrast to conventional cancer therapies that have numerous inevitable side-effects while targeting oncocells. Immunotherapy drugs include checkpoint inhibitors and chimeric antigen receptor T-cell therapy that increase body's capacity to generate cancer-fighting cells, or assist healthy cells in recognising and eliminating

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malignant cells. Targeted antibodies are tailored immune-proteins that target identified cancer cell markers to prevent malignancy, particularly uncontrolled proliferation. Antibody-drug conjugates contain anticancer medication that is transported to tumours. Bispecific T-cell engaging antibodies bind both cancer cells and T cells to enhance the speed and efficacy of the immune response. The immune system develops numerous built-in mechanisms, or checkpoints to limit the duration and intensity of the immune response to minimize any unintended damage to the surrounding tissues by the activated T cells. This reduces immunological reaction and guards against inflammation and autoimmune disease. It is primarily accomplished by the increasing coinhibitory receptors to 'switch off' the active T cells[7]. The fate of an activated T cell ultimately is determined by the balance between costimulatory and coinhibitory signals.

Several strategies have been developed to this effect. First, passive therapy that allows T cells to attack cancer cells without direct manipulation, usually by attaching to and altering the intracellular signalling of the surface receptors. One such example is the checkpoint inhibitor monoclonal antibodies that prevent cancer cells from attaching to receptors that inactivate T cell. Second, direct alterations *in vitro* to assault cancer cells when administered to a patient on active therapy. One such example is the removal of T cells from the body, their expansion and genetic modification making them more tumour-associated antigens (TAAs) specific, and finally administering to the patient. A similar strategy is used in cancer vaccines, occasionally in the context of antigen-presenting cells or viral vectors, wherein TAA is recognized and reintroduced with adjuvants to elicit an immune response.

Respiratory tract has a defense mechanism that prevents the inhaled medication particles from reaching the lungs and to remove or inactivate them if deposited, making the pulmonary drug administration relatively complex. In addition to these behavioural obstacles of poor adherence and subpar inhaler technique, pulmonary medication delivery is also adversely affected by the mechanical, chemical and immunological barriers. The pulmonary route presents enormous opportunity, frequently meeting unmet therapeutic needs. Due to such benefits offered, the difficulties it presents are worthwhile to address. Using inhaler devices and formulations that efficiently transport the medication to the lungs, proper inhaler technique and enhanced patient education are counter-strategies.

There are very few over-the-counter inhaled medications and these tend to be used for fairly standard medical conditions like pain management or diabetic therapy. Numerous inhaler devices are available to deliver inhaled medications. Pressurized metered dosage inhalers, dry powder inhalers and nebulizers are often used to deliver inhaled medications. Systems with alternative aerosol generating principles are occasionally applied to deliver particular therapeutics. Dry powder inhaler formulations containing paclitaxel-based nanocarriers like micelles, solid lipid nanoparticles and nanocrystals specifically target lung cancer cells by binding to folate receptors and enhancing its residence time in the lungs[8]. Large porous microparticles laden with oridonin delivered through the lungs exhibited a potent antilung cancer impact[9].

Given the myelosuppressive and immunosuppressive properties of chemotherapy, the concept of combining it with immunotherapy may seem illogical, yet it has strong preclinical support. In fact, chemotherapy-induced myelosupression also reduces regulatory T cells, myeloid-derived suppressor cells and tumour-associated macrophages. Further, cytotoxicants can work in concert with immune checkpoint inhibitor to strengthen the immune systems by promoting the killing of the immunogenic tumour cells, increasing the production of neoantigens in oncocells and increasing the levels of proinflammatory cytokines in the tumour microenvironment. The most promising and advanced clinical trials involving chemoimmunotherapy combinations are being probed on nivolumab, pembrolizumab and atezolizumab[10].

Human monoclonal antibodies or polyclonal convalescent plasma, by acting on the SARS-CoV-2 spike protein, could eliminate virus and improve infection outcome in susceptible individuals or established COVID-19 cases. Monoclonal antibodies as a strategy differ from convalescent plasma in the sense that it operates against defined targets (such as the spike protein) with high degree of neutralisation. The foundation of immunotherapy is, providing immediate humoral immunity against virus thereby reducing the viral load on the one hand and inducing immunomodulation through Fc-γ receptors on the other, both contributing to reducing the severity of illness and improving the health. The role of Fc-γ receptors in treating COVID-19 however is contentious as literature also refers to it as a disease-enhancing factor.

A combined treatment of bamlanivimab and etesevimab decreased COVID-19-associated hospitalisation, reduced the virus load and the duration of illness and decreased death cases in high-risk ambulatory patients. However, in the seronegative (at baseline) hospitalized cases, monoclonal antibodies, casirivimab and imdevimab (REGEN-COV) combination reduced the mortality. Early administration particularly before the antibodies develop endogenously, antiviral immunotherapy could manifest strong therapeutic potential. Although it may not be beneficial as endogenous antibody production mounts later, theoretically it might be helpful in immunocompromised cases that remain seronegative with virus load being persistently detected.

Contaminated surfaces in public places like hospital, park, public transport and school are common source of infection[11]. Nano-based surface coating could potentially prevent infection[12,13]. Incorporating nano-based antimicrobials into the personal protective equipment could protect healthcare personnel[14]. The issue of developing antiviral resistance, common with many conventional antiviral drugs, may be decreased through nanoformulations[15]. To increase the efficiency and reduce the treatment dosage period, it could be designed with controlled-release property and specific tissue targeting. Currently being practised to treat other infectious diseases, such approach could augment multidrug therapy[16].

Drug delivery scientists across the world are working on creating novel carriers and drug delivery techniques to combat against viral infections, and to create safer and more effective vaccinations against SARS-CoV-2 variants like omicron. Particularly, mRNA-based vaccines depend on effective drug delivery mechanisms. The intricate mRNAs molecules have difficulty in entering the cells on their own as they rapidly degrade in body fluids. Lipid nanoparticle technology for effective delivery of mRNA into cells and into the cytoplasm, where it can be translated by ribosomes into the necessary protein, has been a major advance[17,18]. COVID-19 vaccines are consequently heavily dependent on the complementary use of drug delivery and nanotechnology. Development of safe and effective mass vaccinations depends on combining the strengths of mRNA and the drug delivery vehicle.

The intricate interactions between a nanomaterial and the biological system under varying physiological state (nanoparticles reaching the blood circulation in the body which is an intricate matrix of

ions, small molecules, proteins and cells) make it challenging to predict the in-vivo behaviour of nanoformulations[19]. Protein–nanoparticle and protein–protein interactions regulate the protein adsorption on the nanoparticles[20]. Interacting with proteins, nanoparticles form protein corona that is dictated by the physicochemical properties of nanoparticles[20]. As protein corona gives the nanoparticles a new biological identity with modified physicochemical properties, determining biological responses of nanoformulations is vital instead of the native nanoparticle traits[21]. In light of this, the success of a nanomedicine shall be dependent on due characterisation of the protein corona. To provide teeth to the global efforts to combat the pandemic, the healthcare systems may be empowered through the 'One Health' model approach with state-of-art interventions in drug delivery on one hand and a fool-hardy IoT-based remote surveillance system, additionally employing cutting-edge IT such as the artificial intelligence and deep learning platforms.

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