Exploring the potential of micro-nano composite structures for COVID-19 vaccines and beyond

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The coronavirus disease 2019 (COVID-19) pandemic has emphasised the crucial role of vaccination in mitigating the spread of the disease.[1] While several severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been authorised, most of them are administered through intramuscular injections.[2] Although these vaccines effectively elicit systemic immune responses, they do not provide immediate protection at the respiratory tract, which is the primary site of viral infection.[3, 4] To overcome this limitation, researchers are actively investigating the potential of intranasal or nebulised vaccine candidates.

Intranasal or nebulisedn vaccines have the advantage of inducing localised immune responses in the respiratory tract, including the production of secretory immunoglobulin (Ig) A and IgG.[3, 4] This may enhance the first-line defence against SARS-CoV-2 and potentially reduce the severity of COVID-19 symptoms. Inhaled vaccines have shown the ability to induce comparable antibody responses to intramuscularly injected vaccines but at lower doses.[5, 6] However, the challenge lies in formulating these vaccines in liquid form, which requires cold chain transportation and storage and often necessitates multiple doses or booster vaccinations.

To address these challenges, researchers are striving to develop dry powder vaccines suitable for single-dose inhalation. The goal is to create vaccines that maintain their structure and effectiveness after lyophilisation, have controlled aerodynamic particle sizes for optimal lung deposition, and provide sustained release profiles for continuous antigen stimulation.

One approach involves the use of micro-nano composite structures to develop dry powder vaccines. Professor Wei and his colleagues[7] have employed pentameric cholera toxin B subunit as a mucosal adjuvant, along with trimer-forming peptides to create self-adjuvanting cholera toxin B subunit-based self-assembled nanoparticles (CNPs). These CNPs carry the SARS-CoV-2 receptor-binding domain on their surface, which enhances their uptake by antigen-presenting cells. Smaller particles are more likely to be exhaled along with airflow, whilst larger particles tend to deposit in the superficial lung. Therefore, the CNPs are encapsulated within porous poly(lactic-co-glycolic acid) microcapsules with desired aerodynamic size (2–4 μm), allowing for efficient dry powder aerosol delivery to the alveoli. As the poly(lactic-co-glycolic acid) microcapsules degrade over time, they release the CNPs in a sustained manner, resulting in potent T cell and B cell responses (**Figure 1**).

Preclinical studies utilising this micro-nano composite vaccine have demonstrated promising results. A sole dosage of the vaccine induced elevated levels of IgG and IgA production in mice, hamsters, and non-human primates, offering effective protection against SARS-CoV-2. Furthermore, an engineered "mosaic iteration" of the vaccine displayed potential in responding to anticipated co-circulation of multiple strains and inhibiting transmission of the omicron variant.

The use of micro-nano composite structures in COVID-19 vaccines offers several advantages. These structures enable the development of dry powder vaccines with adjustable size from nanoscale to microscale that can be administered through inhalation, providing localised immune responses in the respiratory tract. Furthermore, this approach provides good storage stability and shows only negligible changes in the aerodynamic diameter of microcapsules and in the hydrodynamic diameter of the encapsulated vaccine nanoparticles after one month of storage. Additionally, encapsulating the vaccine nanoparticles in microcapsules allows for controlled release. As the microcapsules

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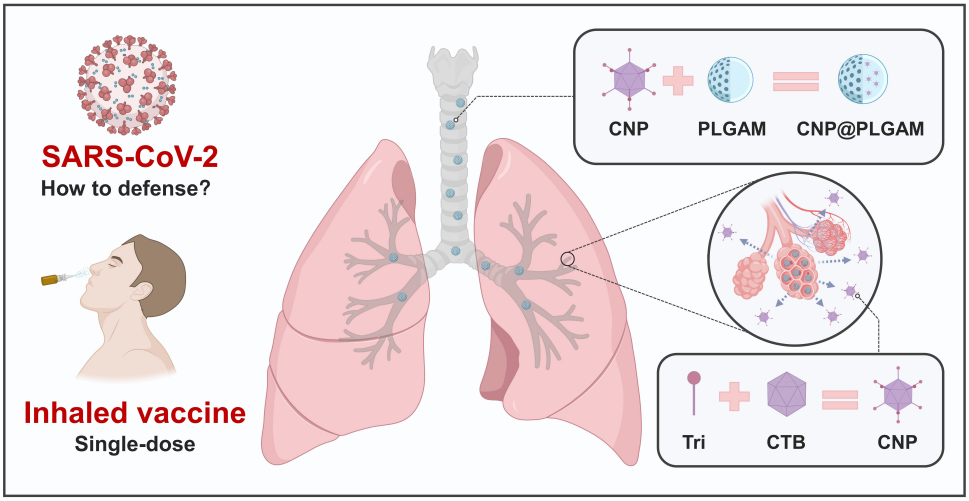

Figure 1. Schematic illustration of the structure and delivery of CNP@PLGAM. Created with BioRender.com. CNP: CTB subunit-based self-assembled nanoparticle; CTB: cholera toxin B; PLGAM: poly(lactic-co-glycolic acid) microcapsules; SARS-CoV-2: several severe acute respiratory syndrome coronavirus 2; Tri: trimer-forming peptides.

gradually degrade, the vaccine nanoparticles are released in a sustained manner and can be taken up by antigen-presenting cells, leading to long-lasting immune responses.

Looking beyond COVID-19 vaccines, micro-nano composite structures hold significant promise in various medical applications. The exceptional properties of these structures, such as controlled release, targeted delivery, and enhanced stability, can revolutionise drug delivery systems, diagnostics, and regenerative medicine. For instance, micro-nano composite carriers have been used to address the difficulties of drug delivery in joints, with functions including "targeting cartilage extracellular matrix", "penetrating cartilage", and "inducing cellular phagocytosis".[8]

Micro-nano composites also find applications in diagnostic and imaging techniques. Incorporating magnetic nanoparticles into tissue adhesive microspheres allows for long-term magnetic resonance imaging monitoring.[9] These composite-based contrast agents provide improved signal intensity, better tissue targeting, and increased stability, enabling more accurate disease diagnosis and monitoring.

In the field of tissue engineering and regenerative medicine, the size and porosity of microspheres can be intentionally modified to mimic the characteristics of natural tissue and facilitate the differentiation of stem cells into a specific lineage.[10] Moreover, by constructing micro-nano composites, it is possible to eliminate harmful factors within the microenvironment, thus creating a favourable condition for the survival of stem cells during the deposition process.[11] The incorporation of bioactive molecules, such as growth factors, further enhances the regenerative potential of these materials.[12, 13]

In conclusion, the analysis conducted by the author suggests that the exploration and utilisation of micro-nano composite structures in COVID-19 vaccines offer significant potential to enhance vaccine efficacy and overcome the limitations of intramuscularly administered vaccines. These structures enable the development of dry powder vaccines that can induce localised immune responses and provide sustained antigen stimulation. This could potentially lead to improved immune responses and increased protection against the virus. Moreover, micro-nano composites hold great promise in various medical applications, including drug delivery, diagnostics, and regenerative medicine. Owing to the progress in research within this field, there is a strong indication that further advancements and applications of micro-nano composites can be expected. These advancements will ultimately contribute to enhancing patient outcomes and furthering medical treatments. However, additional research is needed to fully explore the potential of micro-nano composites in medical applications. Future studies could focus on understanding the long-term effects and biocompatibility of these composites, as well as optimising their manufacturing processes and exploring novel applications in other areas of medicine. Furthermore, investigating the potential of functionalising micro-nano composites with various therapeutic agents and developing targeted delivery systems holds great promise for future medical applications. In conclusion, further research is required to fully harness the potential of micro-nano composites in improving medical treatments and outcomes, and to explore their broader applications in the medical field.

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Conflicts of interest statement
The authors declare no competing financial interests.

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