Inhaled hydrogel-based microspheres for management of COVID-19: A new Sweeper biological platform

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The cytokine storm caused by SARS-CoV-2 infection threatens the condition of patients, even leading to death. In a recent issue of Matter, Prof. Wenguo Cui and co-workers have prepared lung-sweeper inhaled hydrogel microspheres for intratracheal neutralization of COVID-19 and cytokine storm calming, which could be applied for antiviral tissue regeneration, drug delivery, and disease diagnosis.

Looking back through human history, it has been a fight against viruses, such as smallpox, influenza, and more recently, COVID-19. Researchers from various fields developed different strategies to fight against COVID-19. Different from the traditional routes of administration, such as intravenous injection, researchers from Shanghai Jiao Tong University (Prof. Wenguo Cui’s group) ingeniously prepared inhaled microfluidic hydrogel microspheres that can significantly reduce SARS-CoV-2 infection effectiveness and neutralize proinflammatory cytokines.

In the battle between humans and viruses, both sides developed various strategies for winning. The viruses’ propagation mode, replication period, and mutation can create a pandemic. On the human side, the standard defense methods are anti-viral drugs, vaccinations, and hormonal drugs. However, these defense methods have limitations, such as side effects, limited effectiveness, long research periods, and expensive research-development cost. Therefore, humans have to discover various strategies to fight against the viruses.

By masterfully mimicking some natural phenomena, we have creatively attained various achievements in the fight against viruses. In this regard, and in the field of bioengineering, Prof. Wenguo Cui’s group mimic the Sweeper. They construct inhaled microfluidic hydrogel microspheres to eliminate cytokine storms and viruses and protect the body system (Figure 1).

For the construction of such a “sweeper,” inspired by SARS-CoV-2 infecting alveolar epithelial cells through ACE2 receptors, the authors genetically modified HEK293 cells with the overexpressing ACE2 receptor and isolated the ACE2-engineered cell membranes. After that, they fused this cell membrane with the cell membrane of pro-inflammatory macrophages, aiming to neutralize pro-inflammatory cytokines and alleviate hyperinflammation of lymph nodes and spleen. Although the fused cell membranes have their unique biological properties, these
membranes exhibit limited capability to accumulate in the respiratory system. Therefore, inspired by the habit of sweeper fishes in the aquarium to attach to rocks and glass to stabilize the body, the authors attached these cell membranes on inhaled microfluidic hydrogel microspheres to improve their accumulation in the respiratory system. Since the deposition site of microspheres is determined by their aerodynamic diameter (Dare) in the respiratory system, for the “sweeper” system to work, the authors must precisely control the Dare of microspheres at 7.89, 6.63, and 4.21 μm. In this way, these microspheres accumulated in the oropharynx, upper airway, and lower airway of the lung lobes, leading to the protection of the whole respiratory tract against the virus and potentially reducing the viral transmission in humans.

The primary food sources of sweepers are excrement and algae, which means that sweepers hardly harm other fishes and purify the water quality. According to the origin of “excrement,” it can be divided into two parts: cellular origin and the sweeper itself. For lung sweepers, the inhaled microfluidic hydrogel microspheres are able to eliminate the “cellular excrement” by neutralizing inflammatory cytokines (such as IL-1β, IL-6, and TNF-α) in the serum and inhibiting apoptosis induced by cytokines in alveolar epithelial cells. Additionally, as for the microspheres themselves, cilia can effectively capture the microspheres in the upper respiratory tract. This capture method requires microspheres to be excreted mechanically via the actions of cilia and coughing, leading to reduced upper respiratory viral loads and potentially reducing the spread of the virus among the population. The remaining microspheres inside alveoli and the microspheres themselves can be decomposed by enzymatic hydrolysis.

Interestingly, such a “sweeper” system can also be the security guard for other fishes. Accordingly, the lung “sweeper” has a similar behavior in the body. Different from the commercially available vaccines, the administration of neutralizing antibody suppresses alveolar viral loads and lung damage with robust infection in the upper respiratory tract, especially in the nasal turbinates. The authors demonstrated that microspheres protected the upper respiratory tract against SARS-CoV-2 infection for 3 days, indicating that microspheres’ inhalation could potentially reduce the viral load in patients in the mild-to-moderate early stages of the infection. However, the level of the reduction is still limited, and whether it reduces the risk of transmission in human needs to be further studied.

Beyond the contribution to the prevention and treatment of COVID-19, the inhaled hydrogel microspheres provide an advanced inhalation carrier with easily modified chemical structure, controlled aerodynamic diameter, and favorable biocompatibility and clearance from a point of view of both bioengineering and pharmaceutical fields. In the future, this innovative technology is expected to pave the way to fabrication of a wide range of inhaled hydrogel microspheres for various applications, such as tissue regeneration, drug delivery, and disease diagnosis.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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Superwetting interface for miscible liquid separation

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Design of superwetting interface can regulate mass transfer in membrane separation. In a recent work published in Matter by Lei Jiang and colleagues, superwetting interface of polar (or nonpolar) porous membrane and low (or high) polar inductive agent enabled polar (or nonpolar) target liquid components to rapidly permeate the membrane but blocked other relatively nonpolar (or polar) liquid components, realizing miscible liquid separation driven by polar/nonpolar interactions.

Superwetting materials demonstrate predominance in a variety of fields such as membrane separation, mainly involving phase separation of immiscible liquids with opposite polarity and discrepant affinity toward porous membrane,1 in which the development occurs from oil-water mixtures, especially emulsions,2,3 to immiscible organic liquid mixtures.4,5 Nevertheless, separation of miscible liquid mixtures is essential in industries mainly for the sake of chemical synthesis, pharmaceuticals, oil production, etc. Traditional membrane separation, such as pervaporation and reverse osmosis based on size sieving and chemical properties of organic molecules, is energy-intensive and time-consuming.6 Studies toward regulating the transfer of molecules through superwetting interface are significant but still rare.7

The difference in the interaction between molecules and an individual membrane with large pore sizes is insufficient to induce opposite mass transfer behaviors. A competitive interplay for the molecules with relatively small polarity difference at a superwetting interface can regulate the interfacial behaviors of miscible organic molecules. In the breakthrough work recently published in Matter, Lei Jiang and colleagues unveiled that the superwetting interface of polar (or nonpolar) porous membrane and low (or high) polar inductive agent can provide synergistic polar/nonpolar interactions formiscible organic liquid separation.8

In the polar/nonpolar interaction-induced superwetting membrane system (PNISMS) (Figures 1A and 1B), toluene (TL) (with low polarity) and dimethyl sulfoxide (DMSO) (with high polarity) were chosen to compose a typical miscible organic liquid mixture. Porous membranes with opposite polarities were constructed by surface chemical modification of flexible inorganic SiO2-TiO2 composite membrane (denoted as STM), in which modifiers included nonpolar long-chain alkylsilane coupling agent hexadecyltrimethoxysilane (C16) and high polar polymer poly(2-methacyrloyloxyethylphosphorylcholine) (PMPC). When inductive agents such as high polar formamide (FA) and low polar n-hexane (HE) were introduced in the PNISMS, the formed superwetting interfaces (C16/FA and PMPC/HE) created competitive interactions of C16 and FA (or PMPC and HE) with TL and DMSO molecules. The low (or high) polar membrane allowed TL (or DMSO) molecules to selectively permeate, while the high (or low) polar inductive agent dragged DMSO (or TL) molecules (Figures 1C and 1D).

For the separation mechanism, the opposite polarity between the porous