Development of inhalant mRNA vaccine delivered with expandable respiratory epithelial cell-derived exosomes utilizing iPS cell technology.

Yuki Yamamoto／HiLung Inc.

Although COVID-19 mRNA vaccines became a game changer reducing severe diseases, effects on prevention from infection itself were relatively insufficient regarding future pandemic preparedness for respiratory infections. To empower mRNA vaccines to further suppress respiratory infections, it may be highly important to induce local immune response in the respiratory tract. Inhalation is a promising option to efficiently deliver mRNA vaccine into respiratory epithelial cells enhancing local immunity, while there remain hurdles in delivery of mRNA into respiratory epithelial cells with novel carriers such as lipid nanoparticles in terms of efficiency, immunogenicity, and toxicity. Exosomes, physiological vesicles, are expected to be an ideal candidate for overcoming such problems, regarding their low cell toxicity as well as tropism to their progenitor cells. Lacking a source of respiratory epithelial cells for scalable production of exosomes is the largest hurdle for consideration of therapeutic development.

HiLung Inc. established a production system for respiratory epithelial cells derived from human iPSC providing them as research tools for respiratory drug discovery including infectious diseases. We succeeded in further expansion of iPSC-derived respiratory epithelial cells based on tissue engineering and culture know-how, which resulted in efficient production of exosomes compared to conventional methods. We also successfully delivered mRNA and induced target protein by using human iPSC respiratory epithelial cell-derived exosomes (HiREC-Ex) as a carrier. In this study, we will establish a novel respiratory virus vaccine platform, where we will use viral antigen mRNA-loaded HiREC-Ex as an inhalant mRNA vaccine. Four research tasks; establishment of HiREC-Ex production, optimization of mRNA loading and delivery into human respiratory epithelial cells, comprehensive analysis of HiREC-Ex, and preclinical PoC as vaccine, will be set to proceed with this project. Finally, we will confirm preclinical PoC using rodent models focusing on not only systemic immunity but induction of local immune response in the respiratory tract. Our goal is development of powerful mRNA vaccines based on enhanced local immunity and lower toxicity as pandemic preparedness prevents respiratory infections.