NTU Singapore and partners develop new inhaled treatment for severe lung infections

Reviewed

Nanyang Technological University, Singapore

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Nanyang Technological University, Singapore (NTU Singapore) is working with China's Southern University of Science and Technology (SUSTech) and Swedish biotechnology company Lipigon Pharmaceuticals AB to develop a new inhaled treatment aimed at helping patients recover faster from severe lung infections.

The treatment is designed to reduce excessive inflammation in the lungs, which can continue even after viruses or bacteria have been cleared from the body.

Infections such as seasonal influenza, Covid-19, severe acute respiratory syndrome (SARS), bird flu and pneumonia trigger the body's immune system to fight off invading pathogens. But in some patients, this immune response becomes overly strong.

When this happens, the lungs become inflamed and fluid can leak from small blood vessels into the air sacs, flooding them. This makes breathing extremely difficult and reduces the amount of oxygen that reaches the bloodstream. The damage may also persist for days or even weeks after the infection has subsided, making the patient feel breathless.

In severe cases, patients develop acute respiratory distress syndrome, a life-threatening condition marked by widespread lung inflammation and fluid build-up.

To tackle this, the new therapy targets a protein called Angiopoietin-like protein 4 (ANGPTL4), which increases during inflammatory stress in the lungs. High levels of ANGPTL4 are associated with increased vascular permeability and fibrosis in injured lung tissue.

Instead of being taken as a pill or injection, the treatment is delivered directly into the lungs by inhalation, similar to how asthma medications are administered. This allows it to act where it is needed most while limiting effects on the rest of the body.

In preclinical studies led jointly by NTU Singapore and SUSTech, the inhaled treatment reduced lung inflammation and fluid build-up in models of bacterial pneumonia and viral influenza.

In experiments, it also reduced lung scarring in a model of pulmonary fibrosis, a chronic disease that stiffens the lungs, and improved breathing.

SUSTech Assistant Professor Li Liang, co-leader of the study, explained that "severe lung infections frequently lead to lung injury driven by excessive host inflammatory responses".

"Our approach focuses on precise modulation of a defined molecular target to preserve lung integrity while maintaining essential immune defence. Following robust preclinical validation across infection and fibrosis models, the programme is progressing into non-human primate evaluation and Investigational New Drug (IND)-enabling development as the next phase of clinical translation," said Asst Prof Li, an expert in human organoids and respiratory diseases.

Co-leader of the study, NTU Associate Professor Andrew Tan, Provost's Chair in Metabolic Disorders at the Lee Kong Chian School of Medicine (LKCMedicine), said the research took nearly a decade and marks an important step towards more targeted treatment of lung injury.

"This long-term research programme lays the foundation for RNA-based treatments for lung diseases and supports Singapore's efforts to strengthen its capabilities in RNA medicine," said Assoc Prof Tan, who is also Vice Dean (Innovation and Enterprise) at LKCMedicine. "By identifying and validating a lung target that can be treated through inhalation, we are helping to position Singapore in the emerging field of RNA therapies for respiratory diseases."

Global and local burden of lung infections

Severe lung infections remain a major global health challenge. Seasonal influenza alone affects up to a billion people each year, with 3 million to 5 million developing serious illness and an estimated 290,000 to 650,000 people dying from respiratory complications annually.

In addition, pneumonia and other lower respiratory infections are among the leading causes of death worldwide, claiming millions of lives each year and placing heavy demands on health systems.

In Singapore, pneumonia is ranked among the top causes of death, accounting for a significant proportion of deaths in recent years, second only to cancer.

More than 10,000 people are admitted to the hospital each year with pneumonia, making it one of the leading causes of hospitalisation.

Before the Covid-19 pandemic, lower respiratory infections, including pneumonia and influenza-related complications in China were estimated to cause between 190,000 and 220,000 deaths annually.

In Sweden, pneumonia and other lower respiratory infections account for roughly 2,000 to 3,000

deaths annually, while seasonal influenza contributes an estimated 300 to 1,000 excess deaths, mainly among elderly populations.

While mortality rates have declined over the past two decades due to improved healthcare access, the absolute burden remains high, given the aging population in all three countries

Giving an independent comment, Professor David Lye, Senior Consultant, National Centre for Infectious Diseases, who is also the Clinical Co-Director of the Respiratory and Infectious Diseases Programme, Lee Kong Chian School of Medicine, said: "While corticosteroid is effective in severe COVID-19 pneumonia in reducing death, the evidence for corticosteroid in bacterial pneumonia and influenza is less convincing. Although the results of the current work are preclinical, any new, clinically proven therapy to reduce lung inflammation as a result of a patient's immune response to the infective agent is positive news towards improving survival in severe pneumonia."

Also commenting independently, Dr Li Guobao, Head of Pulmonary Disease Department III, Shenzhen Third People's Hospital, said the "inhaled therapy could offer a targeted and patient-friendly treatment option".

"The ANGPTL4 antisense therapy is delivered through inhalation, allowing it to act directly in the lungs with minimal exposure to the rest of the body. This supports a good safety profile with fewer side effects," he said. "It is non-invasive and easy to use, which may improve patient compliance. The therapy works by reducing inflammation, repairing the lung barrier and limiting scarring, offering a safer and more tolerable option for conditions such as acute lung injury, severe pneumonia and pulmonary fibrosis."

Research study done with compound from Lipigon

Lipigon Pharmaceuticals AB provided the compound used in the study and is working with NTU and SUSTech for translational development, which will help pave the way forward for future therapeutics.

> *We are encouraged by these new preclinical data, which add to the growing body of evidence supporting the potential of RNA-based therapies to protect lung tissue in the context of severe pulmonary disease. Severe lung diseases represent a substantial and largely unmet global medical need, and it is our foremost commitment to develop innovative treatments that can make a meaningful difference for patients facing these life-altering conditions. These findings strengthen our confidence in the biological rationale for this approach and support our ambition to advance this RNA therapy into clinical evaluation."*

Early safety studies showed that when delivered by inhalation, the treatment largely remained in the lungs, with minimal distribution to other organs. This localised approach may allow higher concentrations at the site of injury while limiting potential side effects elsewhere in the body.

Supported by NTU Innovation and Entrepreneurship initiative, a joint patent has been filed by the partners, covering the inhaled therapeutic platform. They are now conducting further studies to support regulatory requirements and future clinical trials.

If successfully developed and approved, the inhaled therapy could offer a new treatment option to limit lung injury and reduce long-term complications in patients recovering from severe respiratory infections.