Researchers propose host-directed therapy to stimulate immune system to eliminate tuberculosis

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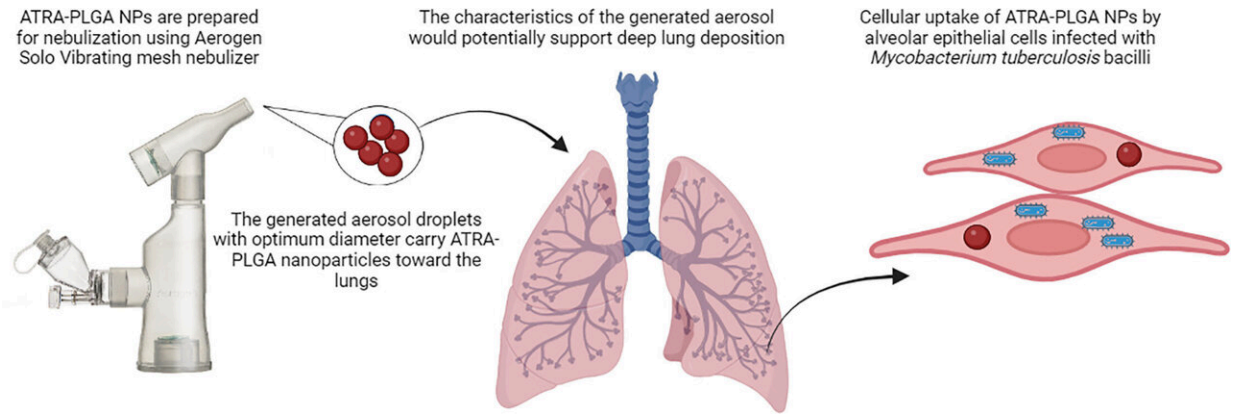

Credit: *European Journal of Pharmaceutical Sciences* (2024). DOI: 10.1016/j.ejps.2024.106734

Tuberculosis (TB) is the world's deadliest bacterial disease and most commonly affects the lungs. Recent years have seen an increase in drug-resistant TB cases leaving many patients with limited treatment options. The only vaccine—BCG—is relatively ineffective at preventing TB in adults. New treatments are urgently needed.

Now researchers from RCSI University of Medicine and Health Sciences and Trinity College Dublin have investigated the potential for a specific host-directed therapy to stimulate the immune system to

eliminate TB, while minimizing harmful inflammation as one way to help bypass antibiotic resistance and complement existing treatments. Their research was recently published in the *European Journal of Pharmaceutical Sciences*.

The bacteria that cause TB first enter the lungs by inhalation into the alveoli (air sacs). Alveolar epithelial cells line the air sacs serving as a barrier between the external environment and the underlying lung tissue. TB bacteria can invade alveolar epithelial cells and establish a reservoir, allowing them to multiply rapidly and spread to other areas of the lungs.

RCSI and Trinity researchers previously showed that the vitamin A derivative all-trans-retinoic acid (ATRA) is a promising host directed therapy that can stimulate "professional" immune cells such as macrophages to kill TB.

They have tested whether ATRA could have the same effect on infected alveolar epithelial cells. The work was led by Dr. Ahmad Bahlool and Professor Sally-Ann Cryan in RCSI, in collaboration with Dr. Mary O'Sullivan and Professor Joseph Keane from the TB Immunology Research Group in the Trinity Translational Medicine Institute, St James Hospital.

The group in RCSI used a technique called "microfluidics" to manufacture inhalable biodegradable nanoparticles (NPs), containing the vitamin A derivative ATRA, that are small enough to be used in a nebulizer and reach the alveoli in the lung. When tested in the lab in Trinity College the researchers found that NPs containing ATRA, as well as ATRA alone, could enable alveolar epithelial cells to stop the growth of the TB bacteria without having toxic side effects on the cells.

The research shows that, despite their susceptibility to TB infection, alveolar epithelial cell defenses can be boosted by ATRA to efficiently

eliminate the bacteria. The results are promising for future research into ATRA-loaded NPs formulations as inhaled host directed therapies for TB.

Professor Cryan, professor of drug delivery and pharmacoengineering, School of Pharmacy & Biomolecular Sciences, RCSI, said, "This work involved close collaboration between pharmaceutical, clinical and industrial research groups to produce a novel, inhalable nanomedicine that can be easily scaled up for further pre-clinical and clinical testing as an inhaled therapy for TB."

Professor Keane, Clinical Medicine, Trinity College Dublin and St James's Hospital Dublin, said, "This exciting new data contributes a new paradigm of how the body fights tuberculosis. Lung airway cells can now be transformed into potent killers of the tuberculosis bacteria."

More information: Ahmad Z. Bahlool et al, Microfluidics produced ATRA-loaded PLGA NPs reduced tuberculosis burden in alveolar epithelial cells and enabled high delivered dose under simulated human breathing pattern in 3D printed head models, *European Journal of Pharmaceutical Sciences* (2024). DOI: 10.1016/j.ejps.2024.106734

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