昭衍
JOINN

E LIBRARY

EXPLORATION AND OPTIMIZATION OF THE PULMONARY FIBROSIS MODEL

Wu Dongkai, Joinn (Suzhou) Safety Pharmacology Department

Pulmonary drug delivery is a unique and challenging drug delivery mode that can be used to treat lung and systemic diseases. The lung disease model that uses pulmonary drug delivery can simulate the clinical pulmonary drug route. In the process of modeling lung diseases such as pulmonary fibrosis, the modeling drugs are unevenly distributed in the lungs after being administered through the lungs, and the local concentration is either too high or too low, resulting in uneven pathological data with large variation, which does not help explain the test results. To overcome this problem, our laboratory uses oral and nose nebulization exposure system and animal lung micro-liquid nebulization inhalation drug administration system to nebulize bleomycin to construct rat and mouse whole lung fibrosis models or unilateral pulmonary fibrosis models, and to prepare a stable, reliable, and high-quality animal pulmonary fibrosis disease model, improving the uniformity of the model.

Pulmonary fibrosis model construction methods:

1. Mouth and nose inhalation: stable and continuous generation of bleomycin aerosol in singlecavity mode, oral and nose exposure and inhalation of nebulized bleomycin, calculate the delivered dose according to the concentration, volume, and inhalation time of the nebulized bleomycin solution;
2. Intra-airway nebulization drug delivery: deliver drug through micro liquid nebulization inhalation delivery system in animal's lung. After the animal is anesthetized and fixed, the tongue is pulled out, exposing the glottis by laryngoscope. Gently insert the nebulizing needle into the trachea, and quickly push the piston, so the bleomycin is inhaled into the left and right lung lobes in single or double nebulization;
3. Single lung modeling: Lay animal on its side after anesthesia, and slowly inject bleomycin through the airway to prepare unilateral pulmonary fibrosis. C57 mice and SD rats are used. Upon completion of the experiment, the animal is tested for lung function and euthanized for lung histopathological assessment.

A. Partial data of the animal whole pulmonary fibrosis disease model

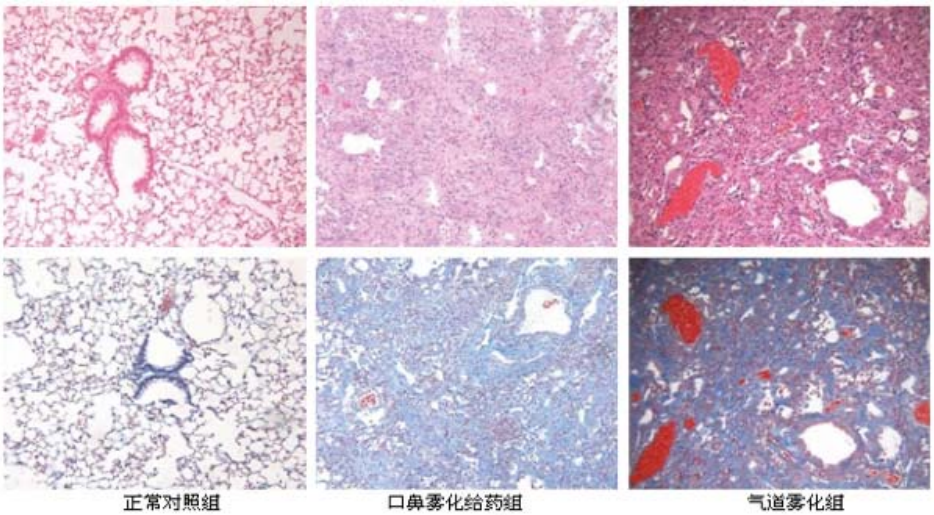


Figure A1: Degrees of lung tissue disease of lung fibrosis model mice, induced by nebulized bleomycin (HE, Masson stain, 100×)

Note: Nebulized bleomycin in both oral and nose nebulizing exposure system and intra-airway nebulization system can induce inflammatory infiltaration and fibrotic lesions in animal lung tissues.

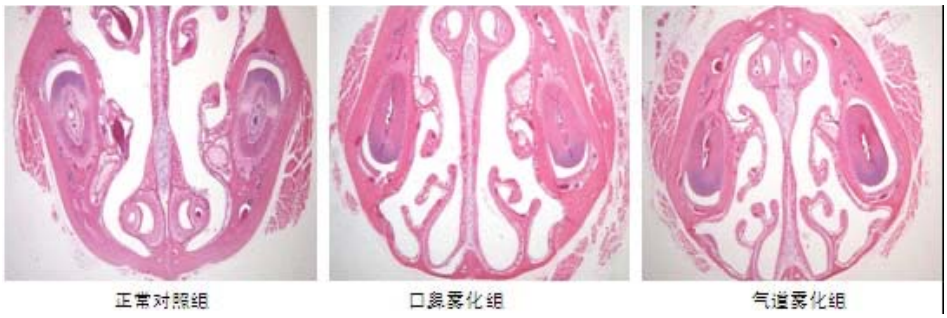


Figure A2: Nasal cavity tissue of lung fibrosis model mice, induced by nebulized bleomycin (HE stain, 20×)

Note: Nebulized bleomycin in neither the oral and nasal nebulization exposure system nor the intra-airway nebulization system causes pathological changes in the nasal cavity tissues.

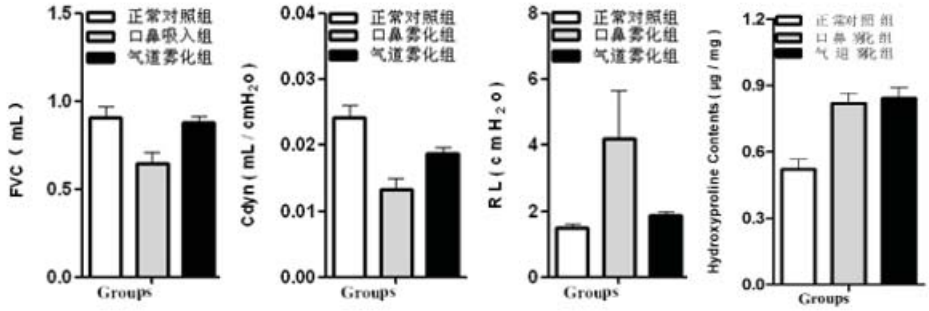
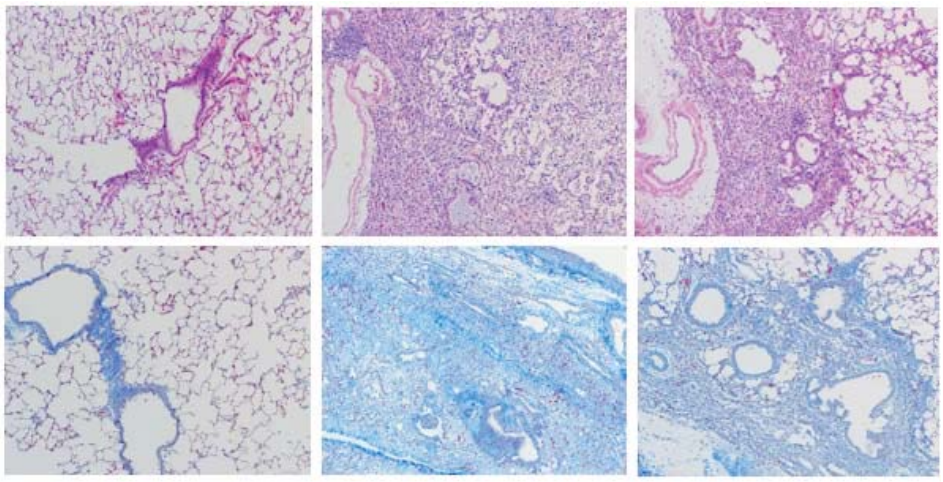


Figure A3: Airway lung compliance, airway resistance and hydroxyproline in pulmonary fibrosis rat model, induced by nebulized bleomycin

Note: Nebulized bleomycin in both the oral and nasal nebulization exposure system and the intra-airway nebulization system can cause a decrease in forced vital capacity, a decrease in lung compliance, an increase in airway resistance, and an increase in hydroxyproline content in lung tissue.

B. Partial data of animal unilateral pulmonary fibrosis model



B1: Pathological changes of left lung fibrosis model in rat, induced by nebulized bleomycin (HE, Masson stain, 200×)

Note: Left: normal control group; middle: model control group; right: commercial control group

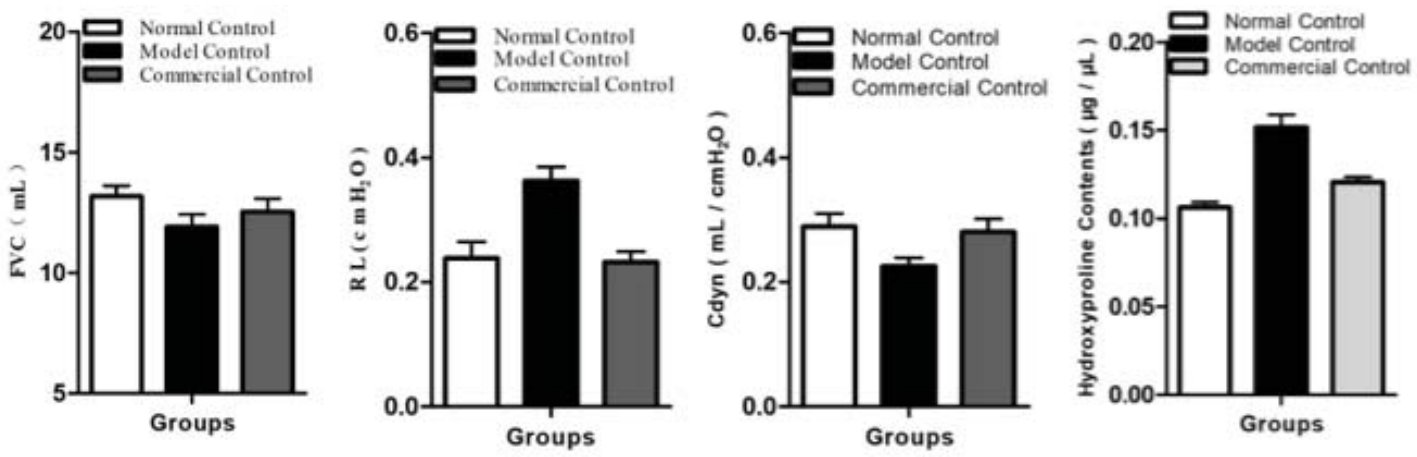


Figure B 2: Airway lung compliance, airway resistance and hydroxyproline in left lung fibrosis rat model, induced by nebulized bleomycin

Note: Intra-airway nebulization system instillation of bleomycin-induced left lung fibrosis model can cause a decrease in forced vital capacity, a decrease in lung compliance, an increase in airway resistance, and an increase in hydroxyproline content in lung tissue

Characteristics of the modeling method of oral and nose inhalation administration: the advantages include: after the animal inhales the aerosol through mouth and nose, the drug can be evenly distributed in the lung lobes; the severity of fibrosis or lung damage in each lobe is relatively consistent; and the relevant indicators of each lung lobe is also relatively consistent. At the same time, there are no diseases like fibrosis in the nasal cavity. The disadvantage is that the operation of this system is relatively cumbersome, requires strong technical expertise, and can be affected by many factors. Skilled personnel are required to operate and control the system. Nebulization requires a large amount of medicine. It's difficult to deliver an accurate dosage; calculation is needed based on the actual nebulization result. In addition, this system is relatively expensive and the test cost is relatively high.

Characteristics of intra-airway nebulization administration: the advantages include: the dosage of the nebulized bleomycin in this system is relatively accurate; it's influenced by fewer factors, and the amount of medicine required is small. Also, the system is relatively low cost. The disadvantage is that the system has relatively high technical requirements. For example, if the speed and strength of pushing the piston are not well-controlled, the drug cannot be fully nebulized, causing an uneven distribution in the lung lobes, which leads to deviations in the relevant indicators among lung lobes. Also, if the nebulization needle is not thoroughly disinfected, it will bring exogenous pollutants into the animal body, which will affect the assessment results. However, these can be solved by multiple intra-airway nebulization administration and thoroughly cleaning and disinfecting the nebulized needle before each administration.

Characteristics of the single-lung modeling method: The advantage is that the animal has a high survival rate (basically no death), with a greater degree of pathological changes in single lung. The disadvantage is that the lung function cannot be evaluated, and the operation is relatively complicated.

In the past two years, we have completed more than ten lung fibrosis model tests in rats and mice and the efficacy assessment of corresponding drugs. The technology of inducing whole lung fibrosis or unilateral pulmonary fibrosis disease model in rats and mice by oral and nasal inhalation or intra-airway inhalation of nebulized bleomycin is stable and reliable. The completed efficacy assessment results also meet customer requirements, helping customers with the RND of new drugs. With the gradual optimization of existing conditions in our organization, we can provide high-quality, stable and reliable animal pulmonary fibrosis models for clients to choose animal lung-related disease models suitable for their test products or indications.

Since the outbreak of COVID-19 in 2019, RND of new drugs intended to treat the new coronary pneumonia or pulmonary fibrosis has been increasing. It is of particular importance to construct a stable, reliable and reproducible pulmonary fibrosis model for drug research related to lung diseases and for new drug assessment.