NOBLE LIFE SCIENCES

Cotton Rat RSV Infection Model

Introduction

RSV is a major human pathogen causing mild to severe respiratory infections in infants and young children, resulting in up to 125,000 hospitalizations and 400 deaths among infants annually. Because treatment options are limited, a significant need exists for economically attractive, viable vaccines and therapeutic agents for normal-risk infants and children.

The cotton rat is considered the model of choice for preclinical development of RSV vaccines and therapeutic agents because:

- Cotton rats are susceptible to non-adapted human RSV and display many features of human pathology.
- Permissiveness to infection with human RSV surpasses that of mice by more than 100-fold.
- The model closely recapitulated the devastating pathological outcome associated with the RSV-vaccine failure in the 1960's.
- The model accurately predicted the success of immunoglobulin prophylaxis (RSVIg - RespiGam®) against RSV bronchiolitis in the newborn population.
- The predictive quality of the model is so high that palivizumab (Synagis®) was advanced to clinical trials based on the results of efficacy and safety studies in cotton rats, bypassing testing in primates. The model also accurately predicted the dose of the drug in human infants.

Applications

- Vaccine development
- Adenoviral vector gene therapy
- Infectious disease pathogenesis

Model Read-Outs Include

- Viral load in nasal tissue
- Viral load in bronchoalveolar fluid
- Viral load in lung homogenate
- Immunohistochemistry
- Tissue pathology

In addition to RSV, the cotton rat has been found to be susceptible to a wide variety of human viral pathogens including influenza. Noble Life Sciences now offers end-to-end solutions for testing the a efficacy of a therapeutic agent against RSV in cotton rat RSV infection model.

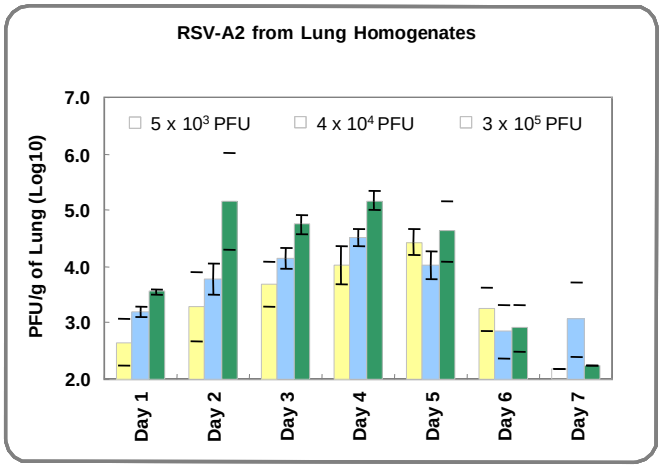
Methodology

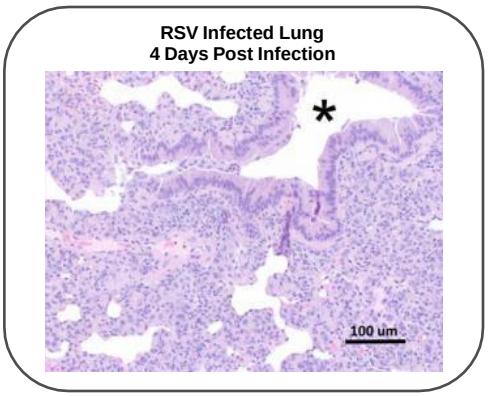
Three groups of cotton rats were infected intranasally with RSV strain A2 at 3 x 10^3, 4 x 10^4, or 3 x 10^5 plaque-forming units (PFUs). The kinetics of viral infection were determined by euthanizing four rats in each group at daily intervals post infections. Lungs were harvested from all euthanized animals. Sections of lung tissue were prepared for H&E staining. The remainder of the lung tissue was homogenized. Viral titers of lung homogenate were determined via plaque assay and qPCR. Bronchoalveolar lavage fluids (BALF) can also be used to follow the course of infection.

To demonstrate the use of this model for testing the efficacy of anti-RSV test agents, one group of four rats was treated with an anti-RSV monoclonal antibody (Synagis) as a test agent. The animals were dosed twice daily at 200 mg/kg and challenged with 4 x 10^4 RSV strain A2. Animals were euthanized on day five and viral titers in the lung homogenates were determined by plaque assay.

Results

Viral titers in lung homogenates of animals infected with RSV increased from day 1 through days 4–5 post challenge and then declined through day 7 (see figure at right). In general, titers in lung homogenates were higher in groups challenged with higher levels of virus.





Lung histopathology is another indicator of morbidity in the cotton rat model. H&E staining of lung tissue sections revealed marked interstitial pneumonia (loss of the normal thin alveolar walls), as seen in figure at left, and inflammatory infiltrates are commonly observed around proliferating bronchioles (note *).

To demonstrate the use of the model for testing the efficacy of anti-viral agents, four animals were dosed with an anti-RSV antibody and then challenged with RSV at 4 x 10^4 PFU. Because the efficacy of test therapeutics and vaccines is best measured at the peak of infection, the animals were euthanized on day 5 and viral titers determined. Animals which received the anti-RSV monoclonal antibody showed a significant reduction in viral burden in the lungs compared to control animals.