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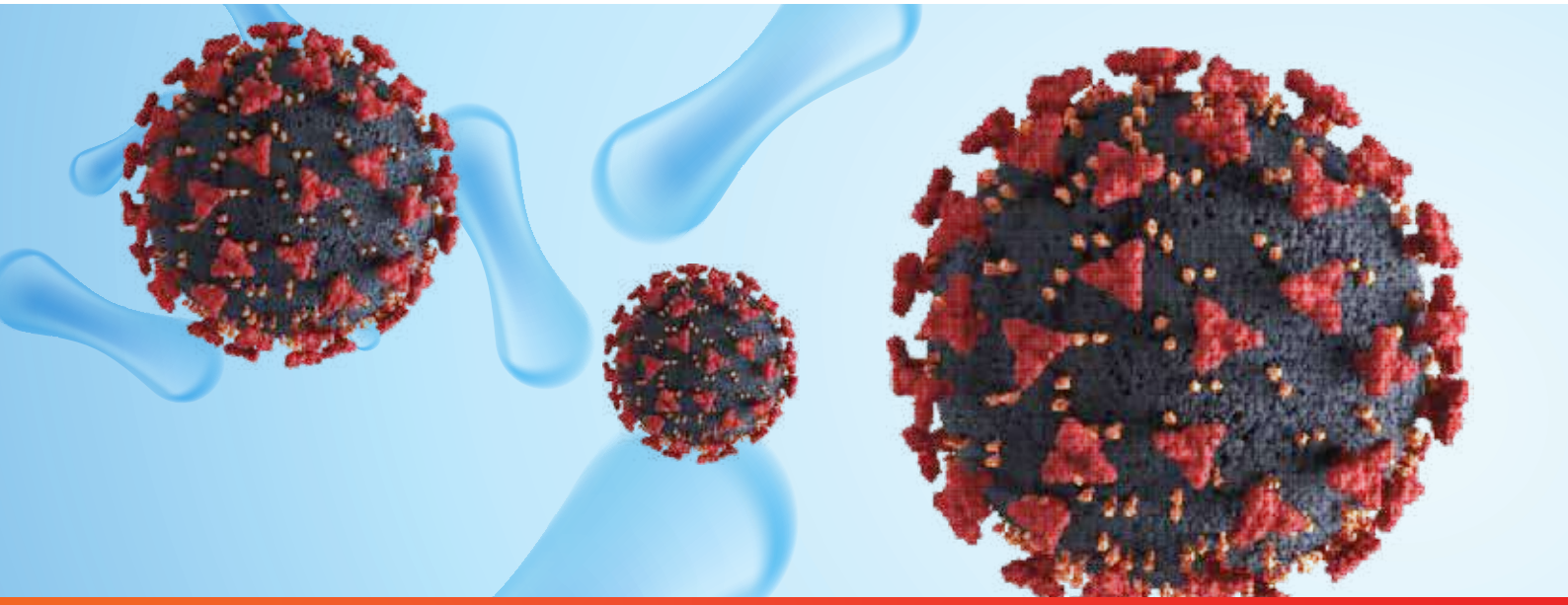


RSV Challenge Model for anti-RSV therapy

The respiratory syncytial virus (RSV) or human respiratory syncytial virus (hRSV) is a common, infectious virus that causes respiratory tract disorders. The virus attacks upper and lower airway epithelial cells, causing inflammation, cell destruction, and airway blockage. RSV infections can range in severity from upper to lower respiratory tract infections and is responsible for over 70% of the cases of bronchiolitis.

RSV is also a leading cause of infant hospitalization and causes significant morbidity. The cold-like symptoms seen in RSV-infected patients appear to be like common flu. However, infants and older adults exhibit symptoms differently. In infants, the RSV infection might occur at age two and remain unnoticed until they exhibit severe symptoms whereas in adults, the symptoms are milder and less easy to identify.

Currently, there is no vaccine against RSV, although prophylactic use of palivizumab is available to prevent infection in high-risk infants. Palivizumab, sold under the brand name Synagis®, is a monoclonal antibody produced by recombinant DNA technology used to prevent severe symptoms caused by RSV infections. Several Pharmaceutical and Biotechnology companies are striving to develop effective RSV vaccines.

The most critical requirement for the development of vaccines against RSV is the development of rodent models which can exhibit the pathophysiology of the disease. Appropriate in vivo rodent models enable accurate preclinical testing of anti-RSV antibodies, small molecules, and vaccines for the treatment of respiratory disease.

Aragen has developed rodent models for pre-clinical testing of a range of drugs for numerous diseases, including oncology, infectious diseases, and neuroscience research services. These models are also suitable for studying the pathophysiology of diseases. Through these in vivo models, Aragen continues to serve pharmaceutical, biotechnology and SMEs in their preclinical efficacy and safety studies.

For RSV, Aragens expert scientific teams have performed pre-clinical testing of range of anti-RSV drugs on in-house mice models.

Here, in this case study we report a non-GLP study performed by the Aragen scientists to evaluate the efficacy of the antibody developed by the sponsor in the RSV challenge mouse models.

Objective of the study

To evaluate the efficacy of XXX antibody (drug) (Test Article) product in comparison to Palivizumab, in controlling viral replication of RSV (Strain A2) in lungs of female cotton rats.

Study Design

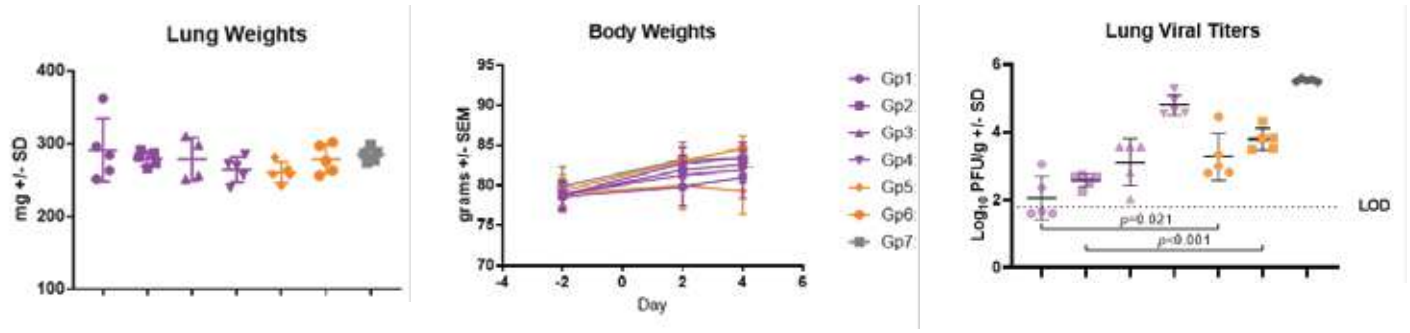
Thirty-five cotton rats (approximately 6-8 weeks old) were separated into 7 groups (N=5/ group).

Gp1	Gp2	Gp3	Gp4	Gp5	Gp6	Gp7
Test Article (4mg/kg)	Test Article (2mg/kg)	Test Article (1mg/kg)	Test Article (0.5mg/kg)	Synagis® 4mg/kg	Synagis® 2mg/kg	Synagis® 2mg/kg

On day -1, rats received a prophylactic intramuscular injection of test article at 4 mg/kg, 2 mg/kg, 1 mg/kg or 0.5 mg/kg or they received a prophylactic intramuscular injection of the control antibody, Synagis® at 4 mg/kg or 2 mg/kg. On Day 0, all animals were inoculated intranasally with 1x105 PFU of RSV strain A2. On day 4, serum, nose and lungs were collected following euthanasia and the viral lung titers were determined by plaque assay.

Observations

The test products and Synagis® exhibited dose-dependent antiviral activity in preventing RSV replication in the lungs of cotton rats infected with RSV A2. Treatment with test products (0.5 mg/kg, 1 mg/kg, 2 mg/kg or 4 mg/kg) significantly decreased viral lung titers compared to treatment with PBS ($p<0.001$). Furthermore, the test products decreased viral lung titers on average 16-fold more than the same dose of Synagis® (4 mg/kg group: $p=0.021$; 2mg/kg group: $p<0.001$).



Conclusion

Aragen successfully completed preclinical investigations of the test compound on in-house female cotton rats. These challenge models are appropriate for preclinical studies of lead drugs developed for the treatment of respiratory disorders or for studying the pathophysiology of RSV infections.

About the author

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Dr. Nagendra Ningaraj has done his Ph.D. from the National Institute of Mental Health and Neurosciences, Bengaluru, and postdoctoral research in Pharmacology and Toxicology from the University of Kansas Medical Centre. He has over 25 years of experience and has previously worked at Acuity Labs, Scintilla Bio-MARC Pvt. Ltd., Memorial Health University, Mercer University Medical School, Global Institute of Medical Sciences, Dr. Reddy's Laboratories, and Vanderbilt University Medical Centre. He was a clinical investigator at PPD before joining Aragen. At Aragen, Nagendra leads the Product Management duties for biological services, with a focus on in vivo studies.