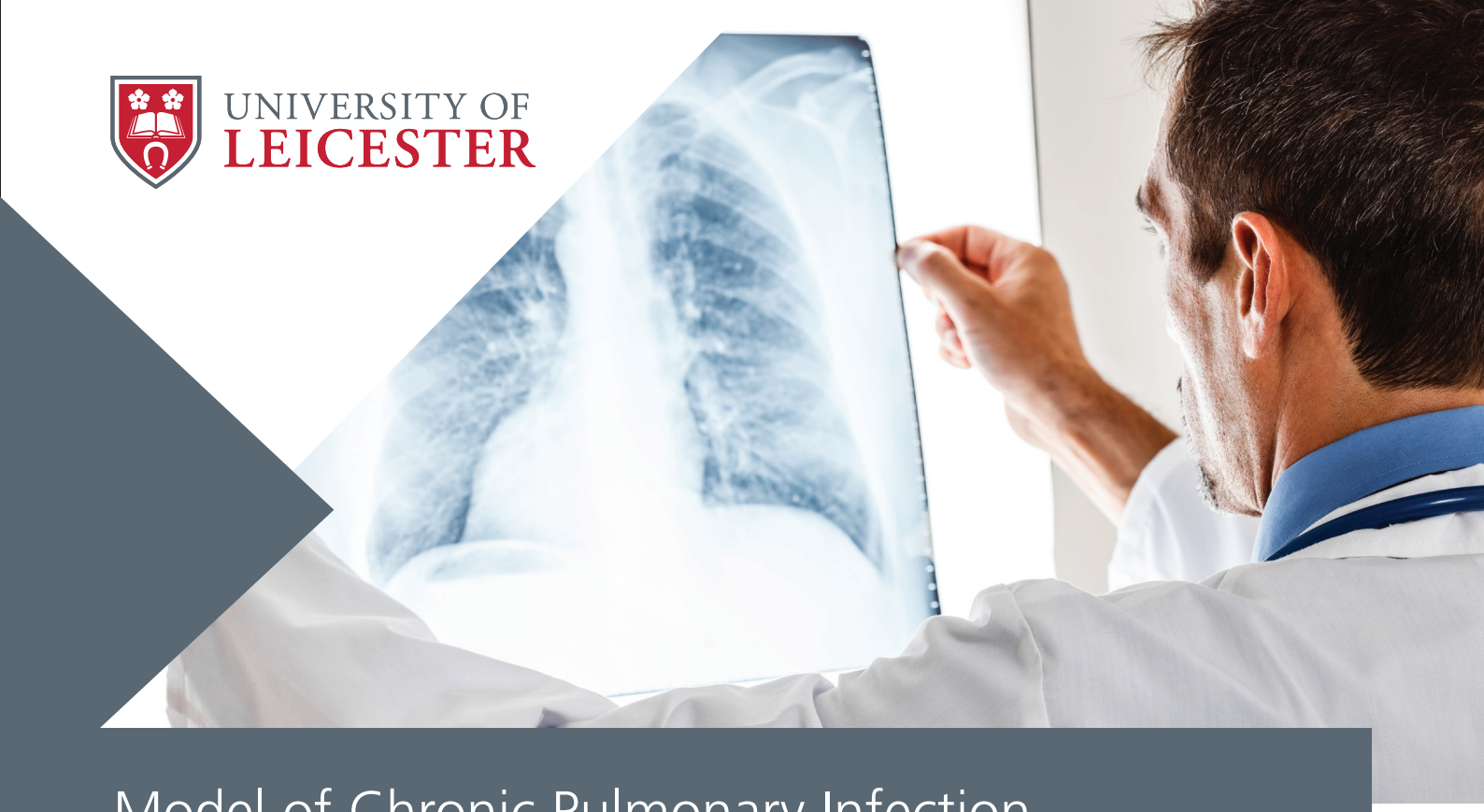
UNIVERSITY OF LEICESTER



Model of Chronic Pulmonary Infection

- **Novel model of chronic pulmonary infection**
- **Robust and repeatable**
- **Clinically relevant**

Challenge

- Asthma and Chronic Obstructive Pulmonary Disease (COPD) are both complex respiratory diseases.
- For the development of new compounds/drugs to treat these diseases, animal models have been used to mimic different aspects of these diseases. However compounds that have shown promise in *in vivo* studies have not always shown the same efficacy in human trials. This could be due to current in vivo models not being able to mimic all aspects of these complex respiratory diseases.
- One aspect of these diseases that has not been successfully modelled is the low level persistent presence of bacterial pathogens in the lungs of some asthma and COPD sufferers.
- The presence of these pathogens in the lower airways has been associated with an increased risk of exacerbation (a worsening of day to day symptoms which is abrupt in onset). Exacerbations reduce the patient's quality of life and are responsible for a large proportion of the economic burden associated with these diseases.
- The three bacterial pathogens most often recovered from the lungs of COPD patients are *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis*.

Solution

A new model of persistent infection in the lungs of mice with the human pathogen *S. pneumoniae* has been developed at the University of Leicester. Key aspects of the model include:

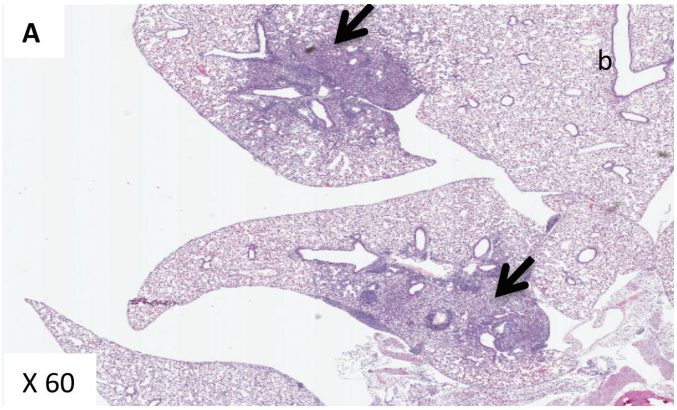
- Viable pneumococci are recovered from the lungs of mice for a minimum of **35 days** after a **single** intranasal instillation of pneumococci.
- **Repeatable and robust:** the same results have been observed every time the model has been run (over 10 separate occasions in 2 different animal units).
- **Few or no** outward disease signs are observed.
- **Clinically relevant,** the serotype of pneumococci used in this model has been associated with COPD exacerbations in humans.
- **Fibroplasia** is observed in the transitional airways from day 14 post-infection with pneumococci.

This is the first time a chronic model of pneumococcal infection in the lower airways has been established. The main challenge with establishing models of respiratory infection with human pathogens in rodents is that the infection is either cleared within a few days or animals succumb to the infection and have to be culled within a few days.

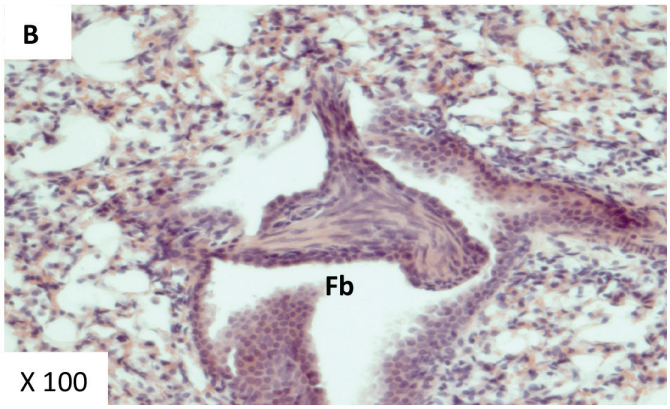
The model has been characterised at a cellular level with differential cell counts and histology. The effects of the infection on lung function has also been assessed with changes in FEV and FRC being observed.

Benefits

- The chronic infection is established with a single intranasal instillation of pneumococci, no other pharmacological interventions or administrations of the bacteria are required.
- The model can be (and has been successfully) combined with other published murine models that mimic phenotypes observed in asthmatics and COPD sufferers.
- This model in combination with other models of respiratory disease could be used to better understand triggers of exacerbation. It also provides a platform for the development and testing of pre-clinical compounds for the treatment of asthma or COPD.
- The model provides a platform for the development and testing of pre-clinical compounds for the treatment of asthma or COPD. It can also be used to assess the effect of drug candidates on underlying infections.



A = Low power at 14 days



B = Higher power at 14 days showing fibroplasia in the airways

A and B are representative of 14 – 28 days post-infection, inflammation is localised and monocytic in nature. Fibroplasia is also seen in the airways; this does not progress to fibrosis but suggests the potential for airway remodelling.

Fb = fibroplasia, b = bronchiole, arrows indicate inflammation

Market

- Respiratory diseases cost the NHS £6.6 billion each year
- Estimates suggest COPD will be the 4th leading cause of death globally by 2030.
- In the US, it is estimated that asthma costs the economy $18 billion.

IP status

A patent application, filed in 2013, is pending.

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