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## BACKGROUND

- Ovine airways are similar in many ways to human airways, making sheep a suitable model for preclinical respiratory drug delivery and efficacy studies (Table 1, Meeusen *et al*, Drug Discovery Today, 2010).

Parameter	Human	Sheep	Rat
body mass	80 kg	45 kg	0.3 kg
nose and/or mouth breathers	mouth/nose	mouth/nose	nose
branching system of trachea-bronchial airways	dichotomous	dichotomous	monopodial
tidal volume (mL)	400 - 616	180 - 405	0.87 - 2.08
respiratory rate (breaths/minute)	12 - 20	15 - 40	85

**Table 1.** Species comparison of airway characteristics shows some of the similarities in human and sheep airways compared to smaller animals such as the rat.

- Models of respiratory disease in sheep include asthma, COPD, pulmonary fibrosis, respiratory infections and lung cancer ([www.allergenix.com.au](http://www.allergenix.com.au)).
- Drug delivery to the airways is becoming an increasingly common method for administration of therapeutics.
- Coughing (tussication) is an unwanted side effect of respiratory delivery that may lead to insufficient deposition of therapeutic doses, non-compliance and adverse inflammatory responses.
- Sheep may provide a cough reflex model that is closely representative to human physiology (Morice *et al*, 2007).

## AIMS OF THIS STUDY:

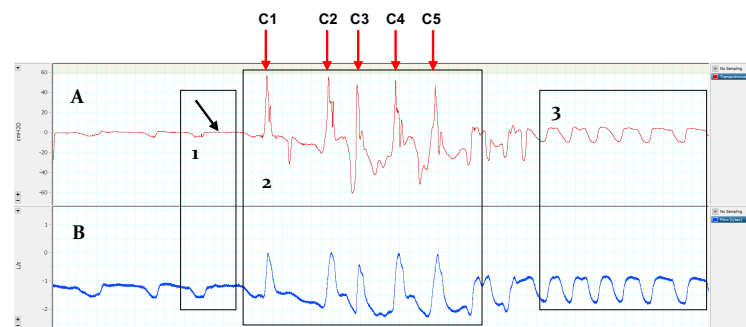
- Demonstrate that tussive agents such as capsaicin and adenosine triphosphate (ATP), which act through different mechanisms, can also trigger a measurable cough reflex in sheep.
- Assess the physiological response to tussive agents delivered into the airways of sheep.

## METHODS

- Airway exposure to capsaicin and ATP were tested in a dose-escalation manner to assess induction of cough responses in sheep airways: dosing continued until a series of 3-5 coughs (C3-5) were induced.
- Bronchoalveolar lavage (BAL) and blood samples were collected before and after dosing for preparation of blood smears and cell counts.

## RESULTS

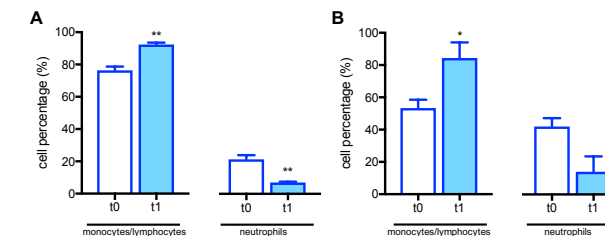
- Aerosolized capsaicin or ATP induced a series of 1-5 audible coughs (C1-C5): effective doses varied between animals.
- Significant 'spikes' were seen in transpulmonary pressure and lung flow rate which closely matched each cough event (Figure 1, box 2).



**Figure 1.** Representative lung function measures of (A) transpulmonary pressure (cmH<sub>2</sub>O) and (B) airflow (L/sec) in sheep following administration of capsaicin (black arrow, box 1). Capsaicin induced a series of coughs (C1- C5, box 2) that were audible, and corresponded with spikes in transpulmonary pressure and airflow, which remained elevated in the short period following the induction of the cough response (box 3).

- Aerosolized challenges with capsaicin or ATP showed little change in BAL leukocyte populations.

- Significant changes in immune cell populations were observed in blood: increase in monocytes/lymphocytes and corresponding decrease in neutrophils in response to ATP and to a lesser degree capsaicin (Figure 2).
- Shift in immune cell populations in blood may indicate a systemic response to the administration of tussive agents.



**Figure 2.** Blood leukocyte populations before (t<sub>0</sub>) and after (t<sub>1</sub>, 30 min) administration of (A) ATP and (B) capsaicin to the airways in sheep. Values are means +/- SEM; significance t<sub>1</sub> vs t<sub>0</sub>: \* p<0.05, \*\*p<0.01; n=4-6 sheep.

## CONCLUSIONS

- Sheep are responsive to tussive agents, similar to humans.
- Clinically relevant and accurate measures of lung function can be assessed in sheep in response to tussive agents.
- Sheep represent a translational model for studying cough responses to drug compounds and antitussive agents.
- Sheep models can be used to study cough response pathways.