RACP
Specialists. Together
EDUCATE ADVOCATE INNOVATE

RACP Foundation Research Awards

FINAL REPORT

Project Title		Does bronchoconstriction in asthma impair anti-viral immunity and promote airway inflammation?
Name		Dr Christopher Grainge
Award Received		2017 The Sir Roy McCaughey Research Establishment Fellowship
Report Date		1 March 2018
Chief Investigator / Supervisor		Dr Christopher Grainge
Administering Institution		The University of Newcastle
Funding Period	Start Date:	1 January 2017
	Finish Date:	1 January 2018

PROJECT SUMMARY

The funding from the Sir Roy McCaughey Research Establishment Fellowship has enabled me to investigate how the airway narrowing that happens during an exacerbation of asthma not only leads to worse symptoms and in some tragic circumstances death, but also has other effects. These initial investigations have been awarded further funding by the National Health and Medical Research Council for the next four years.

Most asthma exacerbations are caused by viral infections, and, during a virus induced exacerbation of asthma, airway narrowing, viral infection and inflammation of the airway occur simultaneously. Previous work has focused on these three elements of asthma, the mechanical forces in the airway, the infection and the inflammation separately, however this Fellowship has enabled me to examine the interaction of these vital events. My early work had strongly suggested that the ability of the lungs to fight off virus is blocked by the airway narrowing that occurs during an asthma attack, and as a result of this, the inflammation in the airway increases, so worsening the patients' asthma and making airway narrowing more likely. This leads to a vicious cycle of bad asthma leading to impaired virus immunity, more inflammation and more airway narrowing.

The award has allowed my research group to confirm and expand these early findings. We have shown that the airway narrowing that occurs during an asthma attack, reduces the ability of the airway cells to fight off viral infections, which likely leads to increased inflammation in the airway. Our job now is to find out how this mechanism works, and how we can restore normal immune function to the airways of asthmatics. Thanks to the Sir Roy McCaughey Research Establishment Fellowship our team has been awarded over $1 million to achieve this over the next four years.

Expanding our understanding of the integration of airway mechanobiology with the function of the immune system and the inflammatory process is vital for deeper understanding and treatment of

asthma exacerbations, both using the current medication in asthma in the most targeted manner, and also in designing new therapies.

PROJECT AIMS / OBJECTIVES

We aimed to determine the molecular mechanisms by which mechanical stress induced TGFbeta expression promotes viral infection in asthmatic airway epithelial cells and the impact this has on innate anti-viral immunity and IFNbeta, interleukin (IL)-25 and IL-33 expression. We actually found that the process was not TGFbeta mediated, contrary to our preliminary data. We did however clearly demonstrate that compression of airway cells, mimicking bronchoconstriction in asthmatics either before or after viral infection, leads to a decrease in interferon beta and lambda production and a concomitant increase in inflammatory markers. This may explain the decreased immune response to viral infection seen in more severe asthma.

SIGNIFICANCE AND OUTCOMES

We demonstrated for the first time that an impairment in innate immunity and an increase in type-2 immune responses results from concomitant viral infection and bronchoconstriction. This is the first time that a mechanical force has been shown to impact on immune function, and may explain the decreased anti-viral immunity seen in some asthmatics.

As a direct result of data obtained using funding from the Sir Roy McCaughey Research Establishment Fellowship our group has been awarded over $1 million by the National Health and Medical Research Council to investigate our findings in more detail over the next four years.

PUBLICATIONS / PRESENTATIONS

Two abstracts accepted at the American Thoracic Society.