

## **Characterisation and treatment of innate immune dysfunction in older people with obstructive airway disease**

During my Ann Woolcock Research Fellowship I have conducted, supervised, and collaborated on a series of important studies exploring the role of the innate immune system in older people with obstructive airways disease (asthma and/or COPD). I have examined a novel mechanism leading to neutrophilic inflammation in obstructive airways disease which is a key discovery in this area and will be generalisable to other neutrophilic airway diseases such as non-CF bronchiectasis, protracted bacterial bronchitis in children, and post-transplant bronchiolitis obliterans.

Since commencing my fellowship I have had considerable grant success with 3 new NHMRC project grants since 2010 resulting from my fellowship work and will now seek to translate the discoveries into clinical practise in severe asthma and COPD. I have also written a chapter The Biology of Neutrophils in the prestigious text book “Middleton’s Allergy Principles and Practise”. In March 2014 I submitted an NHMRC project grant investigating a novel therapeutic target for neutrophilic asthma which is the result of a new collaboration with A/Professor Sandy Hodge in Adelaide and A/Professor Johan Bylund in Sweden.

The ARC Fellowship has significantly advanced my career development. In 2013 I was promoted to Associate Professor (research only) at the University of Newcastle and named the Elsevier Scopus Young Researcher of the Year for Medicine and Medical Sciences. I was appointed the chair of the awards committee for the Thoracic Society of Australia and New Zealand. In 2014 I was appointed the Research Higher Degree Coordinator for the School of Medicine and Public Health.

### **Research Program**

Obstructive airways diseases in the older age group are increasingly common, and the distinction between different diseases can be blurred. In clinical practice distinguishing asthma from COPD in adults older than 55 is problematic because of overlap of many of the features of both diseases. This overlap may result from altered pathophysiology in the elderly,

where the underlying inflammatory reaction in the airways becomes similar in the different conditions as people age.

Ageing is associated with a range of immune system changes. There are well-described changes in both innate and adaptive immunity with ageing. Important inflammatory cells called neutrophils, exhibit decreased capacity to perform some of their vital functions with ageing, which may lead to persistence of infection. Neutrophil responses are typically associated with activation of the innate immune system. The development of age related airway neutrophilia implicates a role for the innate immune response being responsible for this effect

During my fellowship I have investigated how alterations in the innate immune response in older people with airways disease can potentiate the effects of ageing and compare these results with older and younger healthy controls. I have also been examined the effect of a new treatment to determine its ability to reduce airway neutrophils in older people with COPD.

### **1. Characterisation of immune dysfunction in older people with obstructive airways disease**

The obstructive airway diseases COPD and asthma are now major health issues for Australia's ageing population. COPD is a disease of global significance that is a major contributor to mortality and morbidity in older people. The airflow obstruction that characterises COPD is progressive and incompletely reversed by current therapy. This underscores the need to better understand disease mechanisms which would facilitate the search for new treatment modalities in COPD. Airway inflammation is a key element of COPD, and typically involves neutrophilic infiltration of the airways. Neutrophilic bronchitis in COPD is persistent, and remains after the removal of stimuli such as tobacco smoke. The role of airway inflammation in obstructive airway disease of older people is poorly understood. It is likely to be important but also different to younger people because of life-long exposures to particulates such as cigarette smoke or other immune stimuli such as infections.

Persistent neutrophilic bronchitis is also a feature of other chronic airway diseases; bronchiectasis, allergic bronchopulmonary aspergillosis, and the neutrophilic subtype of asthma. This suggests there may be a common mechanism contributing to persistent airway neutrophilia in these diseases. I have previously described a self-perpetuating neutrophil

activation cycle (NAC) in neutrophilic asthma and hypothesised its existence and the involvement of an important immune system receptor (toll like receptor 2) in other obstructive airway diseases characterised by neutrophilic inflammation. This cycle is activated by toll like receptor 2 stimulation and persists *via* positive feedback interactions between important neutrophil proteins (CXCL-8, NE, and MMP-9) all of which levels are significantly elevated in the airways of patients with neutrophilic asthma.

- Other factors known to influence airway neutrophilia are ageing, smoking, airflow obstruction, infection and corticosteroid use, and these factors are also associated with neutrophilic airway diseases. However, it is unclear to what extent factors such as age and past smoking impact on the persistent neutrophilic bronchitis and NAC in COPD. I have investigated these issues by assessing components of the NAC, and controlling for the effects of age, smoking and airway obstruction in patients with COPD. I have recruited 118 adults and collected induced sputum for bacterial culture and measurement of key inflammatory proteins and genes.

The NAC was enhanced with age, smoking and most significantly in those with COPD. TLR2 gene expression was significantly elevated in those with COPD and was a significant independent predictor of neutrophils in sputum after correcting for age, smoking and airflow obstruction. TLR2 activation led to increased gene expression for TLR2 and the induction of the components of the NAC. The results of this study have been accepted for publication in *Mediators of Inflammation*.

## **2. Treatment of immune dysfunction in older people with obstructive airways disease**

While effective treatments are well established to treat some types of inflammation in asthma and COPD, there are no treatments targeting neutrophilic inflammation. The anti-inflammatory effects of macrolide antibiotics are well-established. Macrolide antibiotics such as azithromycin have separate and distinct antibiotic and anti-inflammatory actions. There is extensive *in vitro* evidence of anti-inflammatory activity of macrolides, and some evidence that they may be efficacious in the treatment of neutrophil mediated airway diseases.

I have conducted a randomised placebo controlled trial of azithromycin therapy for 12 weeks will be undertaken to determine the ability of macrolide treatment in reducing the NAC components as well as bacterial load. In this study I have screened 77 participants and randomized 30 people for the clinical trial of azithromycin therapy in older patients with airways disease.

Nine participants with neutrophilic bronchitis had a potentially pathogenic bacteria isolated and the median total bacterial load of all participants was  $5.22 \times 10^7$  cfu/ml. Azithromycin treatment resulted in a non-significant reduction in sputum neutrophil proportion, CXCL8 levels and bacterial load. The mean severe exacerbation rate was 0.33 per person per 26 weeks in the azithromycin group compared to 0.93 exacerbations per person in the placebo group (incidence rate ratio (95%CI): 0.37 (0.11, 1.21), P=0.062). For participants who underwent chest CT scans, no alterations were observed. In stable COPD with neutrophilic bronchitis, add-on azithromycin therapy reduced severe exacerbations with a non-significant reduction in sputum neutrophils, CXCL8 levels and bacterial load

### **Associate Professor Jodie Simpson PhD**

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#### **ACADEMIC HONOURS, AWARDS AND PRIZES**

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- 2014 Australia China Young Scientist Exchange sponsored by the Australian Government Department of Industry
  - 2013 Elsevier Scopus Young Researcher of the Year, category of Medicine and Medical Sciences
  - 2012 Asia Pacific Society of Respiriology International Meeting Hong Kong, Winner of the Best Oral Paper Presentation
  - 2012 Asia Pacific Society of Respiriology Travel Award
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#### **NATIONAL AND INTERNATIONAL PROFILE**

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I have an established national and an increasingly international research profile in the fields of non-eosinophilic asthma, non-invasive assessment of airway inflammation and neutrophilic airways disease. This is supported by my service at national and international meetings and invitations to speak as outlined below.

#### **Conference Session Chair**

- 2014 TSANZ Chair of Young Investigator Award Finals
- 2014 TSANZ Poster Discussion Chair for Asthma and Allergy SIG
- 2013 TSANZ Poster Discussion Chair for COPD and Asthma and Allergy SIG

- 2013 TSANZ Chair of Young Investigator Award oral presentation
- 2013 TSANZ Poster Discussion Chair for Asthma and Allergy SIG
- 2013 TSANZ Poster Discussion Chair for COPD SIG
- 2012 TSANZ Poster Discussion Chair for Asthma and Allergy SIG
- 2010 TSANZ Research Short Course Coordinator

**Invited speaker**

- 2014 Thesis by Publication - School of Medicine and Public Health research higher degree students
- 2014 Planning for research success. Advice on CV, grant preparation and career. Breakfast session at TSANZ Annual Meeting
- 2013 Centre for Public Health Research Wellington New Zealand. Asthma inflammatory phenotypes across Australia- data from the AMAZES study.
- 2012 Asia Pacific Society of Respiriology Hong Kong – Post Graduate Course in Cell and Molecular Biology

**STUDENT SUPERVISION AND MENTORING**

- 2014-current: Ms Melanie Erriah: Characterising phagocytosis in asthma inflammatory subtypes
- 2012: Mr Kevin Oreo Honours ""Biomarkers for Severe Asthma Phenotype" Class 1
- 2009-14: Mr Lakshitha Gunawardhana, Epigenetic regulation of airway inflammation in non-eosinophilic asthma. **Awarded 2014**
- 2007-14: Ms Hayley See is investigating the *in vitro* response of bronchial epithelial cells and the activation of lymphocytes from COPD patients by infection with rhinovirus, respiratory syncytial virus and *Haemophilus influenzae*. **Awarded 2015**
- 2008-2014: Mr Heng Zhong commenced his PhD in October 2008 studying the *in vitro* response of bronchial epithelial cell and neutrophils to infection with rhinovirus: a comparison of patients with COPD, healthy smokers and healthy non-smokers
- 2007-12: Dr Ama-Tawiah Essilsie completed her PhD in 2012, investigating an animal model of asthma and the role of *Haemophilus Influenzae* infection on inflammatory phenotype.

**RESEARCH GRANTS**

**External Competitive Grants**

Title of project and names of chief investigators	Source and scheme	Date: Duration	Funds
Inflammometry in stable COPD. PG Gibson, VM McDonald, <b>JL Simpson</b> , PAB Wark	NHMRC	2012: 3 Years	\$717,071
Gene expression biomarkers predict severe asthma, inflammatory phenotype, activation	NHMRC	2012: 3 Years	\$449,307

<b>Title of project and names of chief investigators</b>	<b>Source and scheme</b>	<b>Date: Duration</b>	<b>Funds</b>
mechanisms and treatment response. KJ Baines, PG Gibson, <b>JL Simpson</b>			
The pathogenesis of distinct endophenotypes of asthma is underpinned by the collaborative activation of specific PRRs. S Phipps, <b>JL Simpson</b>	NHMRC	2010: 3 Years	\$654,875

### **Internal Grants**

<b>Title of project and names of chief investigators</b>	<b>Source and scheme</b>	<b>Date</b>	<b>Funds</b>
Galectin 3 is reduced in non-eosinophilic asthma and associated with impaired macrophage efferocytosis and sputum neutrophil numbers. <b>JL Simpson</b> , D Arnold	John Hunter Charitable Trust	2014	\$27,512
Faculty of Health and Medicine, Visiting Fellows Grant. <b>JL Simpson</b>	University of Newcastle, Faculty of Health and Medicine	2013	\$4,500
Brawn Fellowship near miss grant. <b>JL Simpson</b>	University of Newcastle, Faculty of Health	2013	\$10,000
Identification of a Specific Biomarker Signature that Identifies Asthma Phenotype. KJ Baines, <b>JL Simpson</b> , PG Gibson	HMRI Project Grant	2011	\$23,700
Transcriptional phenotyping of COPD and the relationship between neutrophilic airway inflammation, airway infection and activation of proinflammatory pathways. KJ Baines, <b>JL Simpson</b> , PG Gibson	John Hunter Hospital Charitable Trust	2011	\$24,000
Molecular Mechanisms of Azithromycin Treatment of Neutrophilic Asthma. KJ Baines, <b>JL Simpson</b> , PG Gibson	John Hunter Hospital Charitable Trust	2010	\$23,025

### **Equipment and Travel Grants**

<b>Title of project and names of chief investigators</b>	<b>Source and scheme</b>	<b>Date</b>	<b>Funds</b>
Miltenyi Biotec GentleMACS Octo Dissociator with Heaters : P Hansbro, P Foster, D Knight, D Van Helden, J Mattes, <b>JL Simpson</b> et al	NHMRC	2014	
Travel Grant. <b>JL Simpson</b>	University of Newcastle	2014	\$2,000
BD FACSCanto II Violet Laser upgrade : P Wark, A Hsu, K Baines, <b>JL Simpson</b> , P Gibson	NHMRC	2013	\$25,000
DP73 Digital colour and monochrome camera : P Foster, A Hsu, P Hansbro, J Mattes, K Baines, <b>JL Simpson</b> et al	NHMRC	2013	\$20,000

Title of project and names of chief investigators	Source and scheme	Date	Funds
Travel Grant. <b>JL Simpson</b>	University of Newcastle	2013	\$1,700
Body plethysmograph respiratory function system : P Gibson, P Wark, L Wood, <b>JL Simpson</b> et al	NHMRC	2012	\$33,076
Travel Grant. <b>JL Simpson</b>	University of Newcastle	2012	\$2,000
Lung Function (Spirometry) testing and sputum induction equipment : P Gibson, <b>JL Simpson</b> , L Wood, K Baines, P Wark, V Murphy	NHMRC	2011	\$10,000

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## PUBLICATIONS

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I have a Scopus H index of 29 (August 2015) and total citations of over 3,000.

### **Scholarly Book Chapters: 1**

- 4 Baines KJ, **Simpson JL**, Gibson PG. The Biology of Neutrophils. Middleton's Allergy- Principle and Practice. 8th Edition Volume 1; Chapter 17: Editors Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske RF, Simons FER. Mosby Elsevier ISBN 978-0-323-05659-5. (2013)

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## RESEARCH OUTPUT

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1. Baines KJ, **Simpson JL**, Bowden NA, Scott RJ, Gibson PG. Differential gene expression and cytokine production from neutrophils in asthma phenotypes. Eur Resp J 2010 35:522-531.
2. Wood LG, **Simpson JL**, Hansbro P, Gibson PG. Potentially pathogenic bacteria cultured from the sputum of stable asthmatics are associated with increased 8-isoprostane and airway neutrophilia. Free Rad Research. 2010;44: 146-154.
3. Baines KJ, **Simpson JL**, Wood LG, Scott RJ, Gibson PG. Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples. J Allergy Clin Immunol. 2011 Jan;127(1):153-160.e9.
4. Wang F, He XY, Baines KJ, Gunawardhana LP, **Simpson JL**, Li F, Gibson PG. Different inflammatory phenotypes in adults and children with acute asthma. Eur Respir J. 2011 Jan 13. [Epub ahead of print]
5. Wood LG, **Simpson JL**, Wark PA, Powell H, Gibson PG. Characterization of innate immune signalling receptors in virus-induced acute asthma. Clin Exp Allergy. 2010 Dec 3. doi: 10.1111/j.1365-2222.2010.03669.x. Epub ahead of print
6. McDonald VM, **Simpson JL**, Higgins I, Gibson PG. Multidimensional assessment of older people with asthma and COPD: clinical management and health status. Age Ageing. 2011 Jan;40(1):42-9. Epub 2010 Nov 17.
7. **Simpson JL**, Gibson PG, Yang I, Upham J, James A, Reynolds P, Hodge S. Impaired macrophage phagocytosis in non-eosinophilic asthma. Clinical and Experimental Allergy. 2013; 43(1): 29-35.

8. McDonald VM, **Simpson JL**, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment of COPD and asthma. *Clinical Respiratory Journal* Accepted Dec 2012
9. Brooks CR, Gibson PG, Douwes J, Van Dalen C, **Simpson JL**. Relationship between airway neutrophilia and aging in asthmatics and non-asthmatics. *Accepted Respiriology* January 2013
10. **Simpson JL**, Baines KJ, Ryan NM, Gibson PG. Neutrophilic asthma is characterised by increased rhinosinusitis with sleep disturbance and GERD. *APJAI* Accepted January 2013.
11. Baines KJ, **Simpson JL**, Gibson PG. *The Biology of Neutrophils. Middleton's Allergy-Principle and Practice 7th Edition Volume 1; Chapter 17 2013: Editors Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske RF, Simons FER. Mosby Elsevier ISBN 978-0-323-05659-5.*
12. **Simpson JL**, McDonald VM, Baines KJ, Oreo KM, Wang F, Hansbro P, Gibson PG. Influence of age, past smoking and disease severity on TLR2, neutrophilic inflammation and MMP-9 levels in COPD. *Mediators of Inflammation* accepted February 22nd 2013.
13. Kaiko, GE, Loh, Z, Spann, K, Lynch, JP, Lalwani, A, Zheng, Z, Davidson, S, Uematsu, S, Akira, S, Hayball, J, Diener, KR, Baines, KJ, **Simpson, JL**, Foster, PS, Phipps, S. TLR7 gene deficiency and early-life Pneumovirus infection interact to predispose toward the development of asthma-like pathology in mice. *JACI* Accepted February 2013.
14. **Simpson JL**, Gibson PG, Yang I, Upham J, James A, Reynolds P, Hodge S. Impaired macrophage phagocytosis in non-eosinophilic asthma. *Clinical and Experimental Allergy*. 2013; 43(1): 29-35.
15. McDonald VM, **Simpson JL**, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment of COPD and asthma. *Clin Respir J*. 2013 Mar 20. doi: 10.1111/crj.12017. [Epub ahead of print]
16. Brooks CR, Gibson PG, Douwes J, Van Dalen C, **Simpson JL**. Relationship between airway neutrophilia and aging in asthmatics and non-asthmatics. *Respirology*. 2013 8(5):857-65
17. **Simpson JL**, Baines KJ, Ryan NM, Gibson PG. Neutrophilic asthma is characterised by increased rhinosinusitis with sleep disturbance and GERD. *APJAI* Accepted January 2013.
18. Baines KJ, **Simpson JL**, Gibson PG. *The Biology of Neutrophils. Middleton's Allergy-Principle and Practice 7th Edition Volume 1; Chapter 17 2013: Editors Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske RF, Simons FER. Mosby Elsevier ISBN 978-0-323-05659-5.*
19. **Simpson JL**, McDonald VM, Baines KJ, Oreo KM, Wang F, Hansbro P, Gibson PG. Influence of age, past smoking and disease severity on TLR2, neutrophilic inflammation and MMP-9 levels in COPD. *Mediators of Inflammation*. 2013;2013:462934
20. Kaiko, GE, Loh, Z, Spann, K, Lynch, JP, Lalwani, A, Zheng, Z, Davidson, S, Uematsu, S, Akira, S, Hayball, J, Diener, KR, Baines, KJ, **Simpson, JL**, Foster, PS, Phipps, S. TLR7 gene deficiency and early-life Pneumovirus infection interact to predispose toward the development of asthma-like pathology in mice. *JACI* 2013 131(5):1331-9.
21. Fu JJ, Gibson PG, **Simpson JL**, McDonald VM. Longitudinal changes in clinical outcomes in older people with asthma, COPD and asthma-COPD overlap syndrome. *Respiration* 2014: 87(1):63-74.



22. Gunawardhana L, Gibson PG, **Simpson JL**, Powell H, Baines K. Activity and expression of histone acetylases and deacetylases in inflammatory phenotypes of asthma. *Clinical Exp Allergy*. 2014;44:47-57
23. Fu JJ, McDonald VM, Gibson PG, **Simpson JL**. Systemic Inflammation in Older Adults with Asthma-COPD Overlap Syndrome. Accepted July 2013 *Allergy, Asthma & Immunology Research*.
24. Gunawardhana, LP, Baines, KJ, Mattes, J, Murphy, VE, **Simpson, JL**, Gibson, PG. Differential DNA Methylation Profiles of Infants exposed to Asthma during Pregnancy. *Paediatric Pulmonology*. 2013 Oct 25. doi: 10.1002/ppul.22930. [Epub ahead of print]
25. **Simpson JL**, Phipps S, Baines KJ, Oreo K, Gunawardhana, LP, Gibson PG. Elevated expression of the NLRP3 inflammasome in neutrophilic asthma. *Eur Resp J* 2013 Oct 17. [Epub ahead of print]
26. **Simpson JL**, Gibson PG, Yang IA, Upham JW, James A, Reynolds PN, Hodge S. AMAZES Study Research Group. Altered sputum granzyme B and granzyme B/PI-9 in patients with non-eosinophilic asthma. *Respirology*. 2013 Dec 23. doi: 10.1111/resp.12213. [Epub ahead of print]
27. Oreo K, Gibson PG, **Simpson JL**, Wood LG, McDonald VM, Baines KJ. Sputum ADAM8 expression is increased in severe asthma and COPD. *Clinical Experimental Allergy*. 2013 Oct 22. doi: 10.1111/cea.12223. [Epub ahead of print]
28. G Peng, **Simpson JL**, Z Jie, Gibson PG. Galectin-3: its role in asthma and potential as an anti-inflammatory target. *Respiratory Research* accepted December 4<sup>th</sup> 2013.
29. Gibson PG, **Simpson JL**, Ryan NM, Vertigan AE. Mechanisms of cough. *Curr Opin Allergy Clin Immunol*. 2014 Feb;14(1):55-61.
30. Baines KJ, **Simpson JL**, Wood LG, Scott RJ, Fibbens NL, Powell H, Cowan DC, Taylor DR, Cowan JO, Gibson PG. Sputum gene expression signature of 6 biomarkers discriminates asthma inflammatory phenotypes. *J Allergy Clin Immunol*. 2014 Feb 27. pii: S0091-6749(14)00111-0. doi: 10.1016/j.jaci.2013.12.1091. [Epub ahead of print]