# SYSTEMIC INFLAMMATION IN OBSTRUCTIVE AIRWAY DISEASE

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MD

A Thesis Submitted for the Degree of Doctor of Philosophy

School of Health and Medicine

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Date Juan-juan Fu

26/05/2014

## ACKNOWLEDGEMENT OF AUTHORSHIP

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each coauthor, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

## ACKNOWLEDGEMENTS

Same casts, different scripts. It seems the same as it was four years ago when I was writing my acknowledgements at the completion of my Masters degree, but what I am now going to say is totally different. Four years ago, I decided to conduct my PhD study overseas, it was not an easy decision to make as I had known little about the world outside. I was so lucky that 'Newcastle' chose me among several candidates, and I chose 'Newcastle' among different offers, because I had learned from the website at that time of the advantages of clinical studies in this centre. Now, I am proud that I have been able to finish the journey and become a qualified PhD scholar.

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## PUBLICATIONS INCLUDED AS PART OF THE THESIS

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2. Wood LG, Baines KJ, **Fu J**, Scott HA, Gibson PG. The neutrophilic inflammation phenotype is associated with systemic inflammation in asthma. *CHEST* 2012; 142: 86-93. (Chapter 3)

3. **Fu JJ**, Baines KJ, Wood LG, Gibson PG. Systemic inflammation is associated with differential gene expression and airway inflammation in asthma. *OMICS* 2013; 17: 187-199. (Chapter 4)

4. **Fu JJ**, Gibson PG, Simpson JL, McDonald VM. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. *RESPIRATION*. 2013 Sep 11. [Epub ahead of print]; PMID: 24029561. (Chapter 5)

5. **Fu JJ**, McDonald VM, Baines KJ, Gibson PG. Airway IL-1 pathway activation and systemic inflammation predict future exacerbation risk in asthma and COPD. Under Review - *THORAX*. (Chapter 6)

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## STATEMENT OF CONTRIBUTION OF OTHERS

I, Peter Gibson, attest that Research Higher Degree candidate, Juan-juan Fu, provided substantial intellectual input and contributions to the study design, patient recruitment, laboratory experimentation, data input, statistical analyses and manuscript preparation/writing for the papers entitled:

1. Fu JJ, McDonald VM, Gibson PG, Simpson JL. Systemic inflammation in older adults with asthma-COPD overlap syndrome. *Allergy, Asthma & Immunology Research*. Accepted for publication on 18th July, 2013; manuscript ID: 2013-0325.

2. Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammation phenotype is associated with systemic inflammation in asthma. *CHEST* 2012; 142: 86-93.

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5. Fu JJ, McDonald VM, Baines KJ, Gibson PG. Airway IL-1 pathway activation and systemic inflammation predict future exacerbation risk in asthma and COPD. Under Review - *THORAX*.

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3. Fu JJ, McDonald VM, Baines KJ, Gibson PG. Airway IL-1 pathway activation and systemic inflammation predict future exacerbation risk in asthma and COPD. Under Review - *THORAX*.

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2. Fu JJ, Gibson PG, Simpson JL, McDonald VM. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. *RESPIRATION*. 2013 Sep 11. [Epub ahead of print]; PMID: 24029561.

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# CONFERENCE PRESENTATIONS & PUBLICATIONS RELATED TO THIS THESIS

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Oral presentation by Juan-juan Fu:

1. Fu JJ, Baines KJ, Wood LG, Gibson PG. Low-grade systemic inflammation is associated with airway neutrophilia in asthma. Respirology (2011), 16 (Suppl. 2), 205.

2. Fu JJ, Baines KJ, Wood LG, Gibson PG, Scott HA, Wood LG. Systemic inflammation mediates airway neutrophilia via the regulation of IL-8 receptors mRNA expression. Respirology (2011), 16 (Suppl. 2), 205.

**European Respiratory Society (ERS) Annual Congress 2012.**

Poster presentation by Juan-juan Fu:

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Poster presentation by Vanessa McDonald:

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Oral presentation by Vanessa McDonald:

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Oral presentation by Juan-juan Fu:

Fu JJ, McDonald VM, Baines KJ, Mao B, Gibson PG. Airway IL-1 pathway activation and systemic inflammation predict future exacerbation risk in asthma and COPD. Am J Respir Crit Care Med 189; 2014: A5357.

## LIST OF COMMONLY USED ABBREVIATIONS

| | |
|---|---|
| ACQ | asthma control questionnaire |
| AFO | airflow obstruction |
| AHR | airway hyperresponsiveness |
| ASM | airway smooth muscle |
| BCR | B-cell receptor |
| BDR | bronchodilator responsiveness |
| BDP | beclomethasone dipropionate |
| BHR | bronchodilator hyper-responsiveness |
| BMI | body mass index |
| CAT | COPD Assessment Test |
| CCI | Charlson Co-morbidity Index |
| COPD | chronic obstructive pulmonary disease |
| CRP | C-reactive protein |
| CVD | cardiovascular disease |
| C2R | chromotrope 2R |
| eCO | exhaled carbon monoxide |
| ELISA | enzyme-linked immunosorbent assay |
| eNO | exhaled nitric oxide |
| ER | emergency room |
| EPR | expert panel report |
| $FEV_1$ | forced expiratory volume in one second |
| FVC | forced vital capacity |
| GO | Gene Ontology |
| GINA | Global Initiative for Asthma |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |

| | |
|---|---|
| HADs | Hospital Anxiety and Depression Scale |
| HRQoL | health-related quality of life |
| ICD | International Classification of Disease codes |
| ICS | inhaled corticosteroid |
| IL | interleukin |
| IQR | interquartile range |
| LABA | long-acting beta-agonists |
| LAMA | long-acting anticholinergics |
| LRTI | lower respiratory tract infection |
| LTRAs | Leukotriene antagonists |
| LTs | leukotrienes |
| MCID | minimum clinically important difference |
| MGG | May-Grünwald Giemsa |
| mMRC | Medical Research Council dyspnea questionnaire |
| MMP-9 | metalloproteinase-9 |
| OAD | obstructive airway disease |
| $PC_{20}$ | provocative concentration resulting 20% fall in the $FEV_1$ |
| PEF | peak expiratory flow |
| qPCR | quantitative polymerase chain reaction |
| RCTs | randomized clinical trials |
| ROS | reactive oxygen species |
| SAA | serum amyloid A |
| SABA | short-acting beta-agonist |
| SIRS | systemic inflammation response syndrome |
| SGRQ | St. George's Respiratory Questionnaire |
| TNF-α | tumor necrosis factor-α |
| 6MWD | six-minute walk distance |

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## ABSTRACT

Obstructive airway disease (OAD) such as asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions affecting people of all age and imposing significant socioeconomic burden. Distinct phenotypes and enhanced airway inflammation and immune dysfunction are typical features of OAD and have been widely studied. Airway inflammation has been shown to relate to adverse clinical outcomes such as exacerbations in asthma.

Systemic inflammation, characterized by minor increase in the circulating inflammatory cells or mediators, has been increasingly recognized as an important feature of COPD. The role of systemic inflammation in OAD is not well understood. While systemic inflammation is associated with COPD comorbidity and may be involved in the disease progression in terms of exacerbation and mortality in COPD, its presence in asthma and potentially in asthma-COPD overlap syndrome and the clinical relevance are still unknown. It is also unclear if there is an association between systemic inflammation and airway inflammation, and how this relates to disease progression.

The aim of this thesis was to investigate systemic inflammation in different phenotypes of OAD including asthma and COPD. The proportion of asthma-COPD overlap syndrome increases with age, therefore this specific phenotype was also assessed in the studies in which older patients were recruited in this thesis. The presence and the associations between systemic inflammation and clinical characteristics were assessed in OAD. In addition, the longitudinal changes in clinical outcomes among these different phenotypes of OAD were compared and linked to systemic inflammation. I also examined the association between airway inflammation and systemic inflammation linking to future exacerbation risk and sought to investigate the mechanisms behind the clinical relevance of systemic inflammation in COPD.

The findings of this thesis have extended our knowledge of the inflammatory mechanisms of OAD. Systemic inflammation and airway inflammation are both important features of OAD and relate to clinical prognosis in terms of exacerbation risk. These are important observations that revealed novel inflammatory mechanisms of OAD and have significant clinical implications. Targeting specific inflammatory pathways might provide novel therapeutic strategies for OAD.