The U-BIOPRED Study

An expert interview with Ian Adcock

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Ian Adcock
Ian Adcock is Professor of Respiratory Cell and Molecular Biology and Head of the Molecular Cell Biology Group at the National Heart and Lung Institute, Imperial College London, UK. He also holds an honorary research position at the Royal Brompton Hospital, enabling him to translate the basic research activities into the clinical environment.

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Professor Adcock obtained a degree in biochemistry and physiology from the University of London and later completed a PhD in pharmacology from St Thomas' Hospital, London, on the role of nuclear receptors on sexual dimorphic patterns in the rat. He performed postdoctoral training at the Medical Research Council (MRC) Brain Metabolism Unit with Professors Tony Harmar and George Fink, and in the Protein Science Laboratory at St Georges' Hospital with Professor Brian Austen. He joined Professor Peter Barnes at the National Heart and Lung Institute in 1990 to undertake research on the effects of corticosteroids on inflammatory mediators in asthma and chronic obstructive pulmonary disease (COPD). This remains his major research area, along with a long-term interest in the mechanisms underlying relative steroid insensitivity in severe asthma and COPD.

Professor Adcock is an internationally recognised scientist in the field of airways disease and inflammation. He has authored and co-authored over 230 scientific articles and has served on the editorial boards of several journals. He has worked as an expert member on national grant-awarding organisations including the UK MRC, the US National Institues of Health (NIH), the Australian National Health and Medical Research Council (NHMRC), the French Agence Nationale de la Recherche (ANR), the Norwegian Research Council and the Medical Research Council of Canada. He has served on the European Respiratory Society (ERS) Council and is currently a member of the ERS Executive Committee and Scientific Programme Committee and Head of the ERS Assembly 5 (Airways Disease).

Professor Adcock is a principal investigator in the Medical Research Council/Asthma UK Centre in Allergic Mechanisms of Asthma and in the Wellcome Trust Respiratory Infections Centre. His recent research has been funded by grants from the Medical Research Council, Wellcome Trust, the British Heart Foundation, the Royal Society, the European Union, the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council and industrial collaborators. He is also a principal investigator in the European consortium Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) on mechanisms of severe asthma that is funded through the Innovative Medicine Initiative of the European Union and European Federation of Pharmaceutical Industries and Associations.

Q: Can you tell us a little about the aims of the U-BIOPRED study?

U-BIOPRED is a European consortium of over 20 academic institutions, 11 pharmaceutical companies and six patient organisations, funded by the Innovative Medicines Initiative (IMI), whose aim is the better characterisation of severe asthma. It is particularly centered on

determining how it differs from person to person, that is, on identifying asthma phenotypes. The project has collected data from 604 adults, including gene expression in blood, bronchial and nasal brushings, biopsies and sputum, as well as proteomics, metabolomics, lipidomics, microbiome and other types of data. The study looks at baseline and longitudinal data, and some patients underwent a viral challenge to mimic an asthma exacerbation. In addition, U-BIOPRED collected data from 282 school-age and pre-school-age children with severe asthma or severe wheeze and their controls.

It has divided the adult project cohort into four clinical phenotypes; severe asthma non-smoking (A), severe asthma smoking (B), mild/moderate asthma (C) and healthy controls (D), as detailed by Shaw et al. in 2015.[1]

Current analytical approaches are examining each individual omics platform to look for differentiators of asthma severity and of asthma subgroups. Eventually we aim to merge the results from each omic individual dataset to produce a composite handprint that should provide better delineation of the mechanisms underpinning different types of asthma.

Q: What have been the most important findings of the study to date?

The published data, so far have confirmed the clustering of clinical features in asthma and obtains similar groups as those reported by the American Severe Asthma Research Program (SARP) consortia; although, the U-BIOPPRED cohort included subjects with more severe asthma and also a smoking group.[2]

We have also clustered subjects according to gene expression profiles and show that different inflammatory mechanisms are associated with similar pathophysiological characteristics, such as sputum eosinophilia. We have confirmed a Th2-associated sputum cluster but also a group of asthmatics with elevated sputum eosinophils due to a non-Th2 mechanism. This suggests that the latter patients will respond to distinct non-Th2 therapeutic approaches. Further work is being undertaken to look at the subgroups of patients seen in each of these clusters.

Q: How can the definition of asthma phenotypes help in disease management?

The switch from a clinical feature-based to a molecular-based definition of asthma should help define patients by the underlying cause of their asthma. This will enable the introduction of drugs targeted towards specific pathways important for the individual patient. It may also provide evidence for those subjects more susceptible to different exogenous environments/stimuli which may be avoided or indicate therapies needed before exposure.

Q: How can blood gene expression help in therapeutic decision-making?

As above. By describing molecular phenotypes of asthma at the site of disease (the airways) we understand the pathophysiological processes that drive asthma for a particular patient or groups of patients. We have shown that by clustering on airway gene expression profiles, we can determine blood biomarkers that are not evident when blood alone is used for clustering.

Q: Can you tell us a little about the recent sub-study comparing bronchial immunopathology in patients with differing asthma severity?

The recent manuscript by Susan Wilson and colleagues looked at bronchial biopsy immunopathology in 158 participants across the U-BIOPRED asthma and control groups.[3] This is the biggest study of its kind and revealed unexpected data. There were fewer mast cells in the submucosa of the asthmatics than with the healthy controls. In addition, the number of CD4+ T-cells was lower in the severe asthma non-smokers than all other groups. Transcriptomic analysis revealed genes that mapped to tissue eosinophils for example. Overall, in asthmatics who were well enough to undergo bronchoscopy and were on recommended therapy, severe asthma exists despite suppressed tissue inflammation within the proximal airway wall. This highlights the need to look at inflammatory cell activation status and the role of airway structural cells in driving severe asthma. ❑

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