A golden age of asthma research

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There has been an extraordinary increase in the understanding of asthma pathogenesis and treatment over the past decade. The *ERJ* is launching a series of reviews to highlight these advances in asthma and identify areas that still require investigation. https://bit.ly/2HrPfpO

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More than a decade ago, there was a widely held opinion among respiratory clinicians and researchers that asthma was, for the most part, solved and not worth investing intellectual or financial capital into research. There was certainly a small proportion of the asthma population (<10%) with severe refractory asthma, who merited attention [1]; but the vast majority of asthmatic patients were well served with the available treatment armamentarium of rapid onset bronchodilators (mainly short-acting inhaled β_2-agonists (SABAs)), inhaled corticosteroids (ICS), or ICS and long-acting inhaled β_2-agonist (LABA) combinations delivered from a single inhaler.

Concerns did exist about the safety of using ICS/LABA combinations [2], mainly because of the evidence for increased risk of asthma mortality from the use of LABA as a monotherapy in asthma [3], later resolved by the results from a number of large safety studies [4] mandated by the US Food and Drug Administration, and there was also controversy about the importance of airway eosinophils in asthma, mainly because of disappointing results from clinical trials which targeted eosinophils using anti-interleukin (IL)-5 monoclonal antibodies [5, 6].

We are delighted to report that this pessimistic view about the importance of research into asthma and its treatment has been followed by a decade or more of unprecedented progress. There has been a major leap forward in understanding of the immunopathology of asthma, particularly in the central role of T-helper type 2 (Th2) cells [7] and innate lymphoid type 2 (ILC2) cells [8] in driving the type 2 airway inflammation seen in many patients with asthma. This process has also become measurable using simple biomarkers (blood eosinophils and exhaled nitric oxide) that are suitable for use in routine clinical practice. Use of these measures in the clinic has established that type 2 inflammation is closely associated with the occurrence of asthma exacerbations [9, 10]. It is now clear that biomarker-directed treatment results in better outcomes as a result of more economical and effective use of treatment [11].

Cytokines produced by type 2 immune cells have been successfully targeted, resulting in the development of a number of biologic therapies for severe eosinophilic asthma, including targeting IL-5 with mepolizumab [12–14], reslizumab [15] or benralizumab [16], and targeting IL-4 and IL-13 with dupilumab [17], and more recently, epithelial-derived cytokines with tezepilumab [18]. These studies confirmed the importance of airway eosinophils in increasing risks of severe asthma exacerbations. Their success depended on the identification of a responsive population using type 2 biomarkers. As a result, severe asthma has become one of the first non-neoplastic diseases to have biomarker directed biological

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therapy. The clear identification of type 2 airway inflammation as a treatable trait in asthma has provided a template for future research in asthma, with the focus on identification of other specific treatable traits [11, 19], which will further enhance the ability to identify the right treatment for the right patient.

Innovations in asthma management have been achieved across the range of severity of asthma. This is, in part, because of the recognition that, while patients considered to have mild asthma have relatively infrequent symptoms and normal lung function, they are known to have evidence of type 2 airway inflammation [20, 21] and therefore may be at risk of severe asthma exacerbations, which can lead to asthma fatalities [22]. Low doses of maintenance ICS can substantially reduce this risk [23, 24], but adherence with maintenance ICS can be difficult for a minimally symptomatic patient to commit to. As a result, many will use a β_2-agonist as reliever medication with the risk of poor outcomes as a result of over-reliance and overuse [25]. A simple pragmatic solution has been to provide inhaled steroids as needed in combination with the rapid onset LABA formoterol [26, 27]. Anti-inflammatory reliever therapy has been shown to be highly effective [28] and is likely to provide an effective solution to the decades old struggle with poor treatment adherence with maintenance treatment in asthma.

The *European Respiratory Journal* has commissioned a series of review articles which highlight some aspects of the remarkable advances in understanding asthma prevalence, pathobiology and treatment over the past decade, and which will also look forward to what maybe ahead. The first of these reviews is published in this issue of the journal. This article is "Trends in worldwide asthma prevalence" by Asher *et al.* [29], which reviews how asthma prevalence is measured, compares asthma prevalence around the world and over time, and the relationships between time trends in asthma prevalence and time trends in hospital admissions and mortality. Other articles in this series include "Asthma management in developing countries", "Childhood asthma: pathogenesis and phenotypes", "Management of mild asthma", "Asthma remission: what is it and how can it be achieved?" and "Treatment options in type-2 low asthma". This series will provide the most current information about asthma, but importantly also focus on areas of research need, to identify important questions that remain unanswered in the heterogeneity of asthma prevalence worldwide, in childhood asthma, in asthma immunopathology and in asthma treatment.

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