Editorial
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While asthma is an old disease, we have come a long way to better understanding this syndrome in the last few years. More recently, there has been a substantial increase in our insights into the immunological mechanisms underlying the pathogenesis of asthma which helped define several phenotypes and endotypes [1]. Along with mapping of several endogenous pathways related to asthma which drive the development of targeted therapies, an increasing number of both external and internal factors inducing or modulating these pathways have also been identified. Our better insight and understanding of ‘modifiable’ factors of asthma will likely improve our approach to its management and thus lead to better outcomes in patients struggling with this disease.

In this issue, Sánchez-García et al. [2], discuss the potential risk factors of asthma from in-utero and maternal exposures to infancy and childhood risk factors and point out the role of few preventive strategies that have been studied or need to be examined. Bontinck et al. [3] report on the effects induced by the exposome, represented by air pollutants, on human well being in general and, specifically, on airways and lung health. Air pollutants including particulate matter, NO$_2$ and ozone which arise from road traffic, industries and other human polluting activities, trigger upper and lower airway inflammation and, thus, can both induce and exacerbate airway diseases such as rhinitis and asthma. In close association with this topic, Steelant et al. [4] report on the epithelial dysfunction and its consequences on chronic respiratory diseases. Furthermore, interesting new insights on both external and internal disease-modifying factors, that is the environmental and ‘endogenous’ microbiome, are addressed by Kozik and Huang [5]. They discuss several recent findings underscoring the accumulating evidence that within defined time-windows in life, microbiota have an important (immune) modifying role in asthma pathogenesis and in shaping the asthma phenotype. In addition, they address the interactions of both indoor microbiome (or aerobiome) and ‘endogenous’ microbiome with environmental factors (e.g. allergens, ozone, etc) and their effects on asthma.

Apart from environmental factors, the clinical expression of asthma in individual patients is composed of multiple, partly overlapping, pathophysiological features and their underlying mechanisms. To implement precision medicine into daily practice, Agusti et al. [6] introduced the holistic concept of treatable traits. The bottom line, this approach comes down to proactive identification of all disease-related components within individual patients that can be treated as part of a personalized management plan. It this issue, Ulrik et al. [7] provide an update on the treatable traits topic, which is being extended to ‘treatable mechanisms’ by uncovering underlying molecular pathways and identifying reliable biomarkers to further refine targeted treatments in individual patients. According to Pitzner-Fabricius et al. [8], regular exercise can improve both symptoms and inflammation [8], while both pulmonary and extrapulmonary comorbidities have a major impact on the course of asthma. Bahmer et al. [9] discuss the complexity of several aspects of airway remodeling, its changes throughout the life-cycle and the urgent need of adequate biomarkers to monitor treatment responses in clinical daily practice. Rogliani et al. [10] discuss the importance of accurately identifying and managing comorbidities especially in patients with uncontrolled disease.

The identification of molecular pathways underlying type 2 asthma has driven the development of several targeted biologics and small molecules. Alarmins [IL25, IL33 and thymic stromal lymphopoietin (TSLP)] act upstream in the inflammatory cascade through activation of dendritic cells and polarizing T cells to produce type 2 cytokines. In addition, they can directly activate several effector cells that play a
Table 1. Unanswered questions to be addressed for novel-targeted asthma therapies (biologics and small molecules)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Which pathway should be (preferably) targeted in the first place by which biologic or SM in an individual patient with an ‘overlapping’ phenotype/endotype?</td>
<td></td>
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<tr>
<td>What is the optimal duration for a given therapy in an individual patient?</td>
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<td>What are the stopping rules for an individual-targeted therapy?</td>
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<td>What is the long-term safety of biologics in the general asthma population and selected special populations (e.g., children, pregnant and elderly patients)?</td>
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<td>What is the feasibility of administering a combination of biologics and/or SM and will that improve the efficacy and maintain safety of the therapies?</td>
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<tr>
<td>Can chronic use of biologics and/or SM alter the natural course of the disease or come close to actually curing the disease?</td>
<td></td>
</tr>
<tr>
<td>Can the use of biologics and/or SM in high-risk individuals prevent the onset of asthma?</td>
<td></td>
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</tbody>
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SM, small molecules.

central role in both allergic and nonallergic asthma. As discussed by van der Veen et al. [11], the asthmatic inflammatory process can be shifted towards either a Th2 or a Th1 environment depending on specific macrophage subtypes present within the airway wall. Gauvreau et al. [12] discuss the potential of targeting TSLP in the treatment of type 2 asthma, while blocking IL33 and IL25 may help to define their respective role in (the treatment of) asthma. In line with principles of precision medicine and the increased emphasis on targeted therapies in patients with severe asthma, Vijverberg et al. [13] discuss the urgent need of clinically reliable biomarkers to guide targeted treatment options in pediatric patients with severe disease. Christenson [14] discusses the use of specific gene signatures representing pathways like Th2 and IL17 to explore the presence of such treatable mechanisms in individual patients.

The development and clinical implementation of targeted drugs into the management of severe asthma allows for the reduction of the overall corticosteroid load in this patient population. Slisz and Vasakova [15] advocate a holistic personalized approach to asthma management, which – apart from pheno/endotyping – should also include the overall (systemic) corticosteroid use with proactive documentation, prophylaxis and treatment of corticosteroid-related adverse events. Timely implementation of the most appropriate targeted treatment options based on adequate biomarkers should be part of the approach.

In summary, our modern understanding of the pathophysiology, triggers and risk factors of asthma have allowed us to ‘think differently’ about this disease. However, despite great progress in unraveling several molecular mechanisms underlying the pathogenesis of asthma and the development of several effective targeted treatment options, several questions remain unanswered (Table 1). Ongoing and future clinical studies should address these questions with the hope that this will help to further shape the precision medicine approach to asthma.

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