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Comparing biologicals and small molecule drug therapies for chronic respiratory diseases

An EAACI Taskforce on Immunopharmacology (TIPCO) position paper

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§ The Task Force of Immunopharmacology (TIPCO) within the Immunology Section of EAACI was established in 2017 to connect scientist and clinicians with the different scientific backgrounds - physicians and basic scientists, pharmacologists, computational biologists - with the task of examining recent breakthroughs on basic mechanisms of immune regulation and review their application in current, upcoming and paradigm-shifting therapeutic approaches for allergy and clinical immunology-related diseases. The different topics for this first position paper, based on comparison of biologicals and small molecule drug therapeutic approaches, were assigned and drafted by authors' subgroups. They were further discussed, developed and compiled during a meeting in Salerno (February 24-25, 2018). The position paper draft was thereafter recirculated and critically appraised until the final version was approved by all Task Force Members.

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Abbreviations

5-LO	5-lipoxygenase
ACO	Asthma-COPD overlap
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALOX5	5-lipoxygenase
BBB	blood brain barrier
c-KIT	CD117/stem cell growth factor receptor/ tyrosine-protein kinase,
CCR2	C-C chemokine receptor type 2
CD	Cluster of differentiation
CDC	complement-dependent cytotoxicity
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COX	Cyclooxygenase
CRTH2= DP2	Chemoattractant Receptor-homologous molecule expressed on T-Helper type 2 cells
CXCL2	Chemokine (C-X-C motif) ligand 2
CXCR2	C-X-C motif chemokine receptor 2/interleukin 8 receptor
CysLT	Cysteinyl leukotriene receptor
DNA	deoxyribonucleic acid

DP1	Prostaglandin D2 receptor 1
DP2	prostaglandin D2 receptor 2
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
FeNO	fractional expired nitric oxide
FEV1	forced expiratory volume in one second
GATA3	GATA binding protein 3
GINA	Global INitiative for Asthma
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GOLD	Global initiative for chronic Obstructive Lung Disease
Gq	guanine nucleotide-binding G protein subunit
GR	glucocorticoid receptor
H1	H1 receptor
IFN	interferon
IgE	Immunglobulin E
IL	interleukin
IL-4Rα	Interleukin 4 Receptor alpha
ILC 1/2/3	innate lymphoid cells group 1/2/3
JAK	janus kinase
LABA	long-acting beta-agonists
LAMA	long-acting muscarinic-agonists
LT1	cys-leukotriene receptor

mAbs	monoclonal antibodies
MAPK	Mitogen-activated protein kinase
MMP	matrix metalloprotease
MR	muscarinic receptor
p110d	phosphoinositide 3-kinasePI3K delta
PDE	phosphodiesterase
PGD2	prostaglandin D2
PI3K	phosphoinositide 3-kinase
PTGIR	prostaglandin I2 receptor
SMD	Small molecule drug
STAT	Signal Transducer and Activator of Transcription proteins
Th1	T helper 1
Th17	T helper cells that produce interleukin-17
Th2	T helper 2
Th9	T helper cells that produce interleukin-9
TNFα	tumor necrosis factor alpha
TSLP	thymic stromal lymphopoietin
TXA2	thromboxane A2
ULABA-	ultra-long-acting beta-agonists
WHO	World Health Organization

Abstract

Chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), together with their comorbidities, bear a significant burden on public health. Increased appreciation of molecular networks underlying inflammatory airway disease needs to be translated into new therapies for distinct phenotypes not controlled by current treatment regimens. On the other hand, development of new safe and effective therapies for such respiratory diseases is an arduous and expensive process. Antibody-based (biological) therapies are successful in treating certain respiratory conditions not controlled by standard therapies such as severe allergic and refractory eosinophilic severe asthma, while in other inflammatory respiratory diseases, such as COPD, biologicals are having a more limited impact. Small molecule drug (SMD)-based therapies represent an active field in pharmaceutical research and development. SMDs expand biologicals' therapeutic targets by reaching the intracellular compartment by delivery as either an oral or topically-based formulation, offering both convenience and lower costs.

Aim of this review is to compare and contrast the distinct pharmacological properties and clinical applications of SMDs- and antibody-based treatment strategies, their limitations and challenges, in order to highlight how they should be integrated for their optimal utilization and to fill the critical gaps in current treatment for chronic inflammatory respiratory diseases.

Introduction

According to the World Health Organization (WHO), chronic inflammatory diseases are approaching pandemic proportions (1). With regard to respiratory diseases, bronchial asthma is the most common chronic, non-communicable disease among children and affects 358 million people worldwide(2) with 49 millions (3) solely in Europe (4, 5). In 2016, the global prevalence of chronic obstructive pulmonary disease (COPD) was 251 million, placing it as the fourth leading cause of death worldwide (1). The economic cost of asthma across Europe is estimated at €17 billion per year with an annual productivity loss estimated at €9.8 billion (6). In addition, the total direct costs for COPD are estimated at about 3.4% of the total healthcare budget - approximately 38.6 billion Euros (4). Despite this health crisis, current development of new safe and effective therapies for respiratory diseases takes longer, costs more and is less successful than for other diseases (7).

In the past decade, high-throughput technology and systems biology have rapidly expanded our understanding of the molecular networks underlying airway disease pathogenesis, aiding the discovery and better definition of targetable pathways. In this scenario, identification of specific

phenotypic and endotypic determinants of asthma and COPD is one of our major research challenges. We should aim for targeted therapies that fulfil the ambitious goal of modifying the natural course of disease rather than symptom control, yet remaining safe, available and affordable, especially for low-income patients.

Along with the success of biologicals for treating allergic- and other immune-mediated conditions - such as severe asthma, systemic lupus erythematosus, rheumatoid arthritis and cancer - small molecule drug (SMD)-based therapies represent an active field in drug R&D and remain highly sought-after in immune-mediated diseases (8, 9). These two drug classes have powerful and distinct biochemical, pharmacological and clinically effective characteristics as well as features limiting their therapeutic performance and they can be used together to create powerful combinations [Ref. Imai]. The main objective of this position paper from the EAACI Task Force on Immunopharmacology[§] is to compare and contrast the major biologicals and SMD–based therapeutic strategies currently available or under clinical investigation for asthma and/or COPD in order to highlight how their distinctive pharmacological and clinical characteristics apply to therapeutic options. In particular, upon a brief review of the main features of the two diseases, we compare the distinct pharmacological properties and clinical applications of SMD- and biological-based therapeutic strategies - with their specific strengths and limitations - and provide an up-to-date list of compounds and online sources (10). Reviewing pharmacological and clinical data side-by-side reveals common unmet needs for these two drug classes and highlights potential avenues for expanding their therapeutic applications for these chronic respiratory diseases.

1. Phenotypes, endotypes and biomarkers in asthma and COPD: uncovering the complexity of chronic respiratory diseases calls for multiple and targeted therapeutic approaches.

Asthma and COPD are both chronic inflammatory airway diseases, though their natural history, pathophysiology and clinical features differ considerably (Tables 1 and 2). The definitions and treatment guidelines for these diseases are reviewed yearly in GINA (Global INitiative for Asthma) and in GOLD (Global initiative for chronic Obstructive Lung Disease) documents, respectively(4, 11). Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation with several features of both asthma and COPD, although it does not represent a single disease entity (11).

Asthma is usually associated with predominant Th2, ILC2 and Th9-driven cell immune responses as well as effector cells: eosinophils and mast cells. As such, specific key targets for asthma are pathways involved in the “T2” response (that is, an adaptive response driven by the cytokine

milieu produced by Th2 lymphocytes, ILCs and other cell types) such as IgE and IL-4, IL-5 and IL-13 and their respective receptors, as well as the prostaglandin D2 (PGD2) receptor (DP2), also termed chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2) receptor. The 'T2-high' asthma is recognized clinically as severe allergic asthma (IgE-mediated) or severe eosinophilic asthma phenotypes both with recurrent exacerbations and blood and sputum eosinophilia. However, at least half of the patients with asthma have an ill-defined 'T2-low' phenotype (12, 13) and non-eosinophilic airway inflammation has been linked to corticosteroid insensitivity (14). Clustering of clinical features or clinical traits has not clarified underlying mechanisms of asthma as anticipated (15, 16). However, unsupervised clustering based on clinical variables and inflammatory markers has started to reveal T2 and non-T2 subphenotypes of severe asthma (17). Prospective and longitudinal validation of these mechanisms will reveal new targets for future interventions (18).

In contrast to asthma, pathogenic mechanisms in COPD are associated to a greater extent with Th1, Th17, ILC1 and ILC3 cells as well as with neutrophils (8); similarly, clustering on clinical features for COPD that may help to specify management and provide a prognostic outcome are lacking, as no universal consensus regarding their definition and prevalence exists. Clinically, many COPD phenotypes and subtypes of COPD exacerbations have been described (19-21), however clustering across COPD cohorts revealed that the COPD heterogeneity is better characterised by continuous disease traits coexisting in varying degrees within the same individual, rather than by mutually exclusive COPD subtypes (22).

No single biomarker is sufficiently specific and sensitive to predict the progression of COPD, the occurrence of exacerbations, the evolution under treatment or the mortality risk (23). The most widely used biomarkers of airway inflammation in asthmatics are blood eosinophils, FeNO (fractional expired nitric oxide) and induced sputum. Overall, limitations exist for current biomarkers in both asthma and COPD as although they stratify patients, none can effectively predict an individually-targeted-treatment response (24). Advancing our knowledge of disease pathogenesis is pivotal in order to help identifying targetable disease pathways, drive the development and personalized application of targeted therapeutic options, including biologicals and SMDs and extend treatment goals to disease-modifying strategies.

2. Main pharmacological features of biologicals and SMDs for asthma and COPD treatment.

2.a. Current therapeutic approaches: good for many but leaving out too many. The common goal of asthma and COPD current treatment strategies, as recommended by GINA and GOLD, is to control the symptoms and to reduce the risk of exacerbations, lower airways damage, loss of function and drug side-effects (4, 11). Both regimens include controller drugs targeting airflow obstruction and inflammation and reliever drugs during stable disease (11) (Table 3).

The majority of patients with asthma achieve their therapeutic goals with the current guideline-based therapy (25). However, some patients remain refractory to control by current glucocorticoid-based anti-inflammatory therapies even when adherence, proper use of inhaler therapy and co-morbid features have been addressed. Compliance is improved by coupling inhalers with devices providing objective measures of use, developing easier-to-use and more effective inhalers and the use of once-a-day formulations (26, 27) which leads to improved control with conventional therapy. If compliance and inhalation technique are satisfactory, then this group of patients initially labelled as difficult-to-control asthma can fall into the category of severe asthma - also labelled as refractory asthma - that respond poorly to glucocorticoid therapy. Severe asthma exists in ~5% of the asthma population (17) and carries the largest burden of asthma morbidity and costs. For this group of patients, add-on biological therapies at GINA Step 5 are now available such as anti-IgE antibody (omalizumab) for those with high total serum IgE levels with allergic asthma, or anti-IL-5 antibody (reslizumab and mepolizumab) and anti-IL-5 receptor antibody (benralizumab) for those with eosinophilic inflammation defined by high blood eosinophil counts. An anti-IL-4Rα antibody (dupilumab) which is effective particularly in severe eosinophilic asthma (28) will also be available for T2-high asthma. For patients with non-eosinophilic inflammation and non-allergic disease there are currently no targeted therapies available, as their endotypic definition is currently unclear.

For COPD, the stakes are even higher as current anti-inflammatory therapies are not effective and there are no disease-modifying therapies. Current therapeutic goals, besides smoking cessation and clinical reassessment, aim at preventing exacerbations, or reducing their severity, in order to slow disease progression and reduce the mortality rate. The complexity/heterogeneity of COPD pathophysiology and the lack of biomarkers for patient stratification have limited the development of novel targeted therapies (29). Strikingly, none of the biologicals pursued so far has reached approval for COPD, although a large number of SMD and biologicals directed against different targets are currently in preclinical or early-stage clinical development (10). Better endotypic characterization is essential to increase the odds of these drugs progressing through the development process. For example, trials with anti-IL-5 (30) and anti-IL-5Rα antibodies (31) in eosinophilic COPD showed either

a lesser or no reduction in exacerbation rates, respectively, when compared to their effects in severe eosinophilic asthma. This implies that eosinophilic COPD may be mechanistically different from eosinophilic severe asthma.

2.b There is strength in differences: comparison of main pharmacologic characteristics of biologicals and SMDs. Biologicals and SMDs differ not only in terms of size, but also in how they are produced, how they behave, their mode of action in the body and their suitability for certain formulations (Table 4) (32).

Biologicals are large molecular-weight therapeutic agents that are synthesized by living organisms and directed against determinants such as cytokines, their receptors or other different specific targets (33). Biologicals can be monoclonal antibodies (mAbs) or recombinant proteins such as soluble receptors for specific cytokines or mutated cytokines able to bind the receptor without activation. SMDs are defined as single molecules with a molecular weight <900 Dalton. Their structure is simple, well-defined and independent of the manufacturing process used to create them. Any modification is well-characterized and SMDs are mostly produced by chemical synthesis; therefore, identical copies can be made having well-defined physicochemical properties (34). Conversely, the development of biologicals requires relatively complex processes with higher associated monetary costs than SMDs (35), as the production of biologicals undergoes multiple scaling-up, purification and quality control steps (33). The half-lives of biologicals are much longer than those of SMDs, thus they are usually administered every 2-4 weeks (every 8 weeks for benralizumab) via intravenous or subcutaneous routes; SMDs are instead administered once or twice daily. In respiratory diseases a commonly used route for administering SMDs like topical glucocorticoids and bronchodilators is by inhalation, which allows a rapid absorption and onset of action; however, many other SMDs (e.g. leukotriene modifiers, methylxanthines) are administered systemically, mostly by oral formulations, because of their chemical structure or because they target soluble molecules or extra-pulmonary targets - thus making the inhalation route not feasible or desirable. Their low molecular weight and chemical structures allow SMD access to and targeting of intracellular molecules. In contrast, biologicals are directed against extracellular or cell surface-bound targets as they do not cross cell membranes under physiological conditions due to their high molecular weight (36). For the same reason, biologicals cannot cross the blood brain barrier (BBB), thus avoiding potentially undesirable effects on central nervous system (CNS).

SMDs are generally less specific than therapeutic biologicals, although this limited specificity might be potentially advantageous as it may allow inhibition of multiple, clinically relevant signaling pathways at non-toxic levels. Conversely, the capacity of biologicals to target single determinants ensures high specificity and are therefore ideal for 'personalized' or 'tailored' medicine as evidenced in oncology(32).

When SMDs dissolve in the gastrointestinal tract, they are absorbed into the bloodstream via the intestinal wall and can reach almost any part of the body because of their small chemical structure. When administered by inhalation, SMDs have specific pharmacokinetic properties that prevent systemic adverse effects (Online Table 1). Most new-generation topical inhaled glucocorticoids are in fact characterized by low systemic bioavailability, high clearance, local activation and/or strong tendency to form lipid conjugates, resulting in high drug concentrations in lower airway epithelial cells and slow drug redistribution (37). These features are shared by the highly lipophilic long-acting beta-agonists (LABA) and muscarinic antagonists (38, 39). Ultra-LABAs (ULABA) have a high affinity for caveolae, a type of lipid raft, further slowing drug redistribution. Moreover, in contrast to atropine, inhaled antimuscarinics do not pass the BBB, thus sparing the CNS effects. Biologicals, administered parentally, have a target-dependent distribution.

The metabolism of SMDs depends on polymorphisms and metabolic induction of hepatic cytochrome p450, whereas biologicals have an extremely low clearance that does not depend on liver metabolism. Biologicals can be degraded in lysosomes after target binding and internalization, by non-specific phagocytosis of the monocyte/macrophage system whereas SMDs are eliminated by hepatic or renal excretion. Due to their longer half-life and size, there is a greater risk for biologicals than SMDs to evoke an immune response. The use of humanized and human mAbs minimizes mAb immunogenicity (40).

2.c. Nobody is perfect: Limitations and critical issues related to biologicals and SMDs.

The relatively lower specificity of SMDs compared to biologicals carries an increased risk of toxicity. Currently, AEs to SMDs due to off-target effects are increasingly identified in the early stages of drug development by computational analysis (41). However, toxicity has significantly hampered the progression of many MAP-kinase, phosphoinositide 3-kinase (PI3K)δ (or γ) and JAK-inhibitors beyond phase 2 clinical trials in COPD (Table 6) (7, 8, 42, 43) and targeting kinases with SMDs has resulted in unexpectedly modest efficacy in clinical trials. Many factors are thought to contribute to this outcome – redundancy and compensatory mechanisms, multiple isoforms, alternative pathways

(44) and also in this case, lack of patient selection (8). The inhaled route for these SMDs may deliver an effective local concentration with much reduced systemic exposure and AEs (45).

The main AEs specifically related to mAbs (as a class) are infusion reactions and immune-related diseases (such as immune-complex-mediated pathologies, immunogenicity, autoimmunity) while other immunologic effects (antibody-dependent (ADCC) and complement-dependent (CDC) cytotoxicity) can be either an AE or a desired effect. Biologicals approved for asthma are overall very well-tolerated with a favorable safety profile. With omalizumab, used in the EU since 2005, the most frequently reported AEs (≤3%)(46) are injection-site reactions and pain, asthenia, nausea, arthralgia, headache and lower respiratory tract infection. Rare AEs include anaphylactic events, sometimes delayed (≤2/1000 patients/year) (47). Pooled analyses of clinical trials and observational 5-year follow-up studies do not identify any association between omalizumab therapy and risk of malignancy (48, 49). The off-target or indirect effects of omalizumab have been also successfully exploited for treating other immunological diseases, such as chronic spontaneous/chronic idiopathic urticaria, through mechanisms not yet fully understood (50). On a cautionary note, recent studies demonstrate that total IgE levels are inversely associated with the risk of multiple myeloma, B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia (51-53). Moreover, IgE plays a role in the rejection of tumors in murine models (54). The safety profile of anti-IL-5 biologicals, at least within their relatively short clinical use, is also good (55). Online Tables 1a-f list and compare approved biologicals and SMDs drugs with their administration route, formulation, starting dose in adults and provides their bioavailability, metabolism, clearance and half-life.

3. Biologicals and SMDs in asthma and COPD: comparison in therapeutic settings

3.1 Beyond anti-inflammatory glucocorticoids: SMDs as forerunners, biologicals as bearers of biomarker-based approach.

In the 1990s, SMDs including antagonists of the arachidonic acid (AA) pathway [i.e., cys-leukotriene (LT)1 receptor antagonists and to a lesser degree inhibitors of the 5-lipoxygenase (5-LO) pathway], were introduced as the first targeted agents for systemic (oral) use in patients with allergic asthma (56). Following registration (1999-2000), these first-in-class agents were positioned mainly due to strategic considerations rather than for a specific indication in patients with a predominantly leukotriene-driven asthma, whose phenotypic characteristics were not fully clear at that time. Following proof of efficacy in traditional asthma models (56, 57), several of these SMDs proceeded into further clinical development showing modest beneficial effects on clinical outcomes in some patients, but not all (58). Consequently, these drugs were often prescribed by default to patients in whom other therapies proved ineffective with subsequent therapeutic failure (59). This

inadequate approach led to the termination of several drug development programs and probably delayed the launch of monoclonal antibodies by at least 20 years. Patient stratification was increasingly recognised as the prerequisite for a successful targeted approach only with the emergence of the definition of asthma, and later COPD, as heterogeneous diseases with different clinical phenotypes, discrete inflammatory phenotypes and responses to standard therapies (16, 60).

While proof-of-concept studies for SMD like bronchodilators could rely on forced expiratory volume in one second (FEV1) reversibility as a clear indicator of efficacy, biomarkers for drugs targeting airway inflammation were less obvious. In 2009, Woodruff and colleagues identified heterogeneity in the bronchial epithelium transcriptomic signature in patients with mild/moderate asthma - 'Th2-high/ Th2-low'- segregating with responsiveness to inhaled glucocorticoid therapy (12). Th2-derived biomarkers, such as blood eosinophil count and periostin, were further validated and selected as indicators for response to Th2-targeted biologicals, including mAbs targeting IL-5 and IL-13, respectively (61, 62). Indeed, a major difference between biologicals and SMDs is that use of biologicals has been based from inception on patient stratification, initially based on clinical disease entities and subsequently on cellular and molecular biomarkers. Research on SMD-related biomarkers guiding patient stratification is instead lagging behind, possibly also due to the broader spectrum of biological functions influenced by SMDs compared to those impacted by a biological agent. In oncology, patient stratification in clinical trials of SMDs is based on the identification of somatic mutations of kinases or other specific genetic biomarkers of SMD response and resistance. A similar strategy is not directly applicable for SMD/kinase inhibitors in severe asthma or COPD, where an aberrant kinase function is mostly secondary to complex, disease- or even endotype-specific upstream activation events rather than genetically defined alterations.

3.2 Biologicals and SMDs for refractory asthma and COPD: parallel approaches, common goals.

Tables 5 and 6 compare targeted therapies based on biologicals and SMDs, respectively, for asthma and COPD in different phases of development, including some that have been halted. A full description of clinical studies testing biological and SMD approaches in these diseases are beyond our scope and are described in recent comprehensive reviews (63, 64). However, an example of targeting T2-high severe asthma with the two strategies (Figure 1) can be drawn by the use of the FDA/EMA approved anti-IgE (omalizumab) or the anti-IL-5 biologicals (anti-IL-5 mAbs: mepolizumab and reslizumab, anti-IL-5Rα mAb: benralizumab) versus new antagonists of the PGD2 receptor, or CRTH2, which is expressed on Th2, ILC2 cells, eosinophils and basophils (65, 66) that may soon become available (pending approval). Fevipiprant (QAW039), timapiprant or setipiprant are SMDs that bind

reversibly and competitively to CRTH2 (67-69) thereby hinder cell activation by PGD2, the major prostaglandin produced by mast cells to recruit CRTH2+ cells and a primary trigger for bronchoconstriction and vasodilation. In proof-of-concept studies, CRTH2 antagonists abrogated allergic responses mainly blocking Th2-related cytokines, eosinophils and IgE synthesis (70, 71). However, several compounds failed in later development phases, possibly due to lack of phenotype-based patient selection. Only recent studies finally provided specific indication in patients with T2-driven, eosinophilic severe asthma (72, 73). Hence, a better definition of biomarkers of response to CRTH2 antagonists would also allow a direct comparison with biologicals and/or the correct selection of patients for evaluation of combined administration.

Additional biologicals (Table 5) have been developed to treat severe hypereosinophilic asthma, targeting IL-4Rα, IL-5Rα and other inflammatory mediators [IgE, OX40L, IL-4, IL-5, IL-9, IL-13, thymic stromal lymphopoietin (TSLP)] (Figure 1) although with disappointing results for IL-13 (74, 75). Alongside CRTH2 antagonists, SMDs directed against PI3Kδ/γ (leukocyte enzymes involved in neutrophil recruitment and activation (76)), the TSLP receptor, muscarinic receptors, histamine receptors, c-kit and mast cell stabilizers and the DNAzyme targeting GATA3 are all under clinical investigation (Table 6).

Common to most of non-T2, non-eosinophilic asthma (Figure 1, right panel) and to COPD (Figure 2) - two major areas of therapeutic unmet need – is the glucocorticoid-resistant neutrophilic inflammation in the context of heightened oxidant burden. Exposure to air pollutants (mainly active cigarette smoke), viral or bacterial infections and clinically relevant comorbidities form a complex pathophysiology and heterogeneous clinical presentation that hinder the identification of discrete phenotypes and related biomarkers able to guide targeted strategies. Indeed, targeting the migration of neutrophils, which occurs predominantly through CXCR2, the CXCL2/IL-8 receptor, with both SMDs (navarixin and AZD5069) and biological approaches (the anti-IL-8 mAb, ABX-IL-8) have failed in several phase 2 studies (Tables 5 and 6). Biologicals targeting major cytokines– such as IL-1, IL-17, TNFα, GM-CSF - and/or their receptors deemed pathogenetic in neutrophilic inflammation have underperformed in clinical trials (Table 5). In contrast, several biologicals that inhibit neutrophil elastase (alpha1 antiproteinase inhibitors) are in phase 4 post-marketing confirmatory trials in stable COPD. Divergent results are also seen in this area with trials of SMDs targeting an array of secreted metabolites and intracellular enzymes, such as inhibitors of matrix metalloprotease (MMP)-9 (77) and of PI3Kδ; receptor antagonists for thromboxane A2 (TXA2), the primary product of COX-1-dependent arachidonic acid metabolism; several inhibitors of MAPK and JAK-STAT pathways (Table 6).

Also in this case, rather than inferring, on these bases, a lack of pathogenic significance and/or targetability of these molecules and pathways, the efficacy of the biologicals and SMD-based strategies that failed in preclinical or clinical studies will need to be revisited taking into account patient stratification. To achieve this, chronic neutrophilic disease determinants – clinical, physio-pathological and functional – will need further deconvolution by additional basic and clinical studies. They should provide the cellular and molecular biomarkers that align with clinical presentations, to allow the endotype-driven patient stratification necessary for properly testing –and comparing - biological and SMDs' therapeutic responses.

3.3 Biologicals and SMDs: combination strategies in asthma & COPD? The heterogeneity of asthma and COPD pathophysiology lends itself to the use of drug combinations to target different disease determinants. For severe asthma (step 5 GINA), a targeted biological therapy is given as an add-on with conventional SMD therapy with significant glucocorticoid-sparing effects (78). The advent of new biologicals and SMDs should hasten new opportunities for testing associations of these drugs classes, taking advantage of the relative strengths of each approach, in order to improve overall therapeutic efficacy.

To date, no double-blind controlled trial studying the combination of biologicals in severe asthma has been published due to the high cost of each drug. Nevertheless, the effect of their combined administration remains to be investigated. There is a programmed study involving dupilumab and REGN3500, a mAb against IL-33, and a combination of the two drugs for asthma (NCT03112577).

Studies on association of SMDs are limited but promising: a double-blind controlled trial of patients with moderate-to-severe asthma found that co-administration of roflumilast and montelukast was superior to montelukast alone in improving lung function and disease control (79). Combining synergistic bronchodilator and anti-inflammatory properties, dual PDE3/4 inhibitors yielded promising results in phase 2 studies of both asthma and COPD (80). This inhaled combination is under development as maintenance therapy for COPD (phase 2b), while in earlier stages of clinical development for asthma (81). Moreover, ILC2s express both cysLT1 (82) and CRTH2 receptors (65); therefore, blocking both receptors with SMDs could potentially abrogate the downstream inflammatory responses of both pathways (83).

Few examples exist of studies evaluating the combination of SMD- and mAb–based targeted approaches in asthma and COPD, despite the potential advantages for this strategy: first, the non-

overlapping pharmacological properties of the two drug classes may overcome pathway redundancies and achieve a synergistic clinical response. With this rationale, preclinical studies in oncology investigated the combination of biologicals (anti EGFR mAb, cetuximab) and SMDs (tyrosine kinase inhibitors, gefitinib/erlotinib) to target the aberrant activation of EGFR pathway in non-small cell lung cancer (32). The combination was superior to either single agent, yielding stronger inhibition of EGFR and downstream signalling in human tumor cells. Moreover, the combination overcame the resistance to SMDs inhibitors by restoring the inhibition of proliferation of gefitinib-resistant cell lines and achieving growth inhibition of single treatment-resistant tumor xenografts (84). Another advantage, verified preclinically, is that the addition of a biological to an SMD could lower the latter's effective dosage, reducing toxicity while preserving efficacy (85, 86).

Given the large heterogeneity of asthma and especially of COPD pathophysiology, a similar dual approach with a single-target aim may apply to a relatively small patient pool and would need a so-far elusive endotype-driven patient selection. To gain a specific yet multi-targeted approach in this context it may be more relevant to test the combination of biologicals and SMDs targeting different extracellular/intracellular molecules and pathways that converge on a common pathophysiological process. To this end, there are studies for lebrikizumab in combination with glucocorticoids (NCT02099656) or with montelukast (NCT02104674) for asthma. Proof-of-concept studies already exist for this approach in airways disease, since all Phase 3 studies of biologicals in severe asthma have been conducted in the presence of high dose inhaled or oral glucocorticoids. For anti-IL-5 or IL-5Rα there was a reduction or even cessation in oral prednisone use, which indicates that these biologicals could replace oral glucocorticoid use in these patients, thus reducing morbidities and costs associated with its side effects.

Conclusions

Clinical and translational studies, as well as large-scale data and computational approaches are uncovering the cellular and molecular complexity of asthma and COPD. These chronic inflammatory lung diseases carry a major health and economic burden worldwide due to their heterogeneous clinical presentations and demanding therapeutic regimens. The four biological-based, targeted therapies so far approved for allergic or for eosinophilic severe asthma have brought a much needed, safe and well-tolerated treatment to patients previously suffering with refractory disease and, in the case of omalizumab for chronic idiopathic urticaria, have expanded its original indications via off-target effects. Nevertheless, long-term sustainability of treatment with biologicals

remains a concern while several new, highly promising targeted therapies, approached by both biologicals and SMDs strategies, disappointingly failed to complete drug development phases, generally through lack of patient stratification and/or absence of an appropriate predictive biomarker. Despite these setbacks, many strides have been undertaken to shorten the critical period between preclinical research and approval of a new drug, the so-called 'Valley of Death'(87), through new strategies for research and development (88) and increasing collaboration between academia and industry, from biomarker identification to integrated disease approaches (89, 90). The requirement for adequate biomarkers and targeted therapies needs to be effectively addressed by both biologicals and SMD strategies in order to deliver 'the right drug to the right patient' (Table 7).

On the 'right patient' side of this connection, recent meta-analysis of anti-IL-5 therapies for asthma (55) suggests that more basic/translational research and bioinformatics analyses need to be devoted to the identification of outcome-specific biomarkers. These will probably be composite biomarkers, with higher sensitivity/specificity than single markers (91) to assess multiple parameters, such as treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal and biomarkers for children <12 years. It is critical to get a deeper mechanistic understanding of COPD and non-T2 asthma endotypes, to enable endotypic discrimination and the development of targeted therapies for these large, heterogeneous patient populations that lack any disease-modifying therapies. The adoption of appropriate biomarkers, as used for trials of biologicals, also in studies evaluating SMDs will introduce a phenotype/endotype-driven patient selection for this class of drugs as well - ultimately to 'dare to compare' biologicals and SMDs, for example anti-IL-5 with CRTH2 antagonists.

On the 'right drug' side, it is intrinsically difficult to reconcile a single-target approach – ideal for high specificity and low side effects – with the multifactorial pathogenesis and heterogeneous clinical presentations of asthma and COPD that may also vary over time. As discussed, it would be ideal having drugs targeting pathologic pathways that are at crossroads of different clinical presentations, in order to be effective across different phenotypes or in mixed phenotypes. The different outcome of targeting IL-13 versus common IL-13/IL-4 receptor α chain points to existing advantages of such strategy. To this end, it could be worthwhile also to test combinations of several SMDs (e.g. CysLTs/CRTH2 antagonists +/- H1 antagonists or DP1 inhibitors). In this area, increasing understanding of the human kinome – the full complement of human protein kinases -, particularly its activation in structural and immune cells within the airway of patients with COPD or severe asthma, is keenly needed (92). Together with formulation for the inhaled route, it will enable the delivery of

safe and effective inhibitors with powerful anti-inflammatory properties that circumvent systemic side effects (9, 44).

Looking ahead, preclinical studies on single inhibitors targeting multiple molecules are being undertaken for both biologicals and SMDs with the dual IL-4/IL-13 blocking mAbs against their receptor subunit IL-4Rα (dupilumab, Table 5), with bi-specific antibodies, (e.g. dual antagonists for IL-4/IL-13, CXCR3/CCR6 and CCR3/CD300a) (93-95) and with multi-target receptor tyrosine kinase inhibitors, so far developed for anti-angiogenic treatment in lung cancer (96).

At present, however, we should also learn from the preclinical and early-phase clinical studies in the oncology and rheumatology fields that clearly indicate the potential benefits of synergistic effects of biologicals and SMDs (32). Combination of targeted mAbs and SMDs should be studied accordingly in carefully phenotyped patients with chronic inflammatory lung diseases, to maximize the advantages of their complementary approach, outlined in this review. Clearly, increased mechanistic knowledge of biologicals/SMD interactions will be necessary to explore the potential benefits of their combined effect for a personalized treatment in asthma and COPD. Testing drug combinations may require the development of specific funding schemes fostering partnerships among different pharmaceutical industry stakeholders - for example in case of compounds owned by different companies - or through public/private consortia, such as in the Innovative Medicine Initiative (97).

Table 1. Key characteristics of asthma and COPD: pathophysiology

	Asthma	COPD
Main risk factors		
	Atopy	Tobacco smoking
	Allergic rhinosinusitis	Severe alpha-1 Antitrypsin Deficiency
	Respiratory infections	Low lung function in adulthood
Main site of chronic airflow obstruction		
	Large and small airways	Small airways
Pathological features		
	Lower airways	
	Chronic and acute on chronic inflammation	
	Mucus changes (plugs during exacerbations)	Mucus quantitative and/or qualitative changes (plugs during exacerbations)
	Subepithelial basement membrane fibrosis	Peribronchiolar fibrosis
Pulmonary emphysema	Absent in lifelong non-smokers	Sometimes, most in advanced grades
Pulmonary arterial hypertension	Absent	Rare
Key cell types in pathogenesis		
	T2, ILC2, T9	T1, T17, ILC1, ILC3
	B cells	
	Dendritic cells	
	Alveolar macrophages	
	Eosinopils	Eosinophils (in some phenotypes)
	Mast cells	
		Neutrophils
	Epithelial cells	
	Smooth muscle cells	
	Fibroblasts	
	Endothelial cells	
Key mediators and receptors*		
	Adrenaline/β2 adrenergic receptors (ADRB2)	
	Acetylcholine/muscarinic receptors	
	Cortisol/glucorticoid receptor	
	Lleukotrienes/cysLTRs	
		Oxidants
	PGD2/CRTH2	
	IgE	
	IL-4/IL-4Rα, IL-5/IL-5Rα, IL-13	
Changes in lung function		
Airflow limitation	Largely reversible in non-smokers	Largely irreversible
Airway hyperresponsiveness	In most cases	Sometimes
Peak flow variability	High	Low
**** evidence from randomized controlled trials (Phase 3)***		

Table 2. Key clinical features of asthma and COPD

	Asthma	COPD
Clinical features		
Usual age of diagnosis		
	< 40 years old	> 40 years old
Natural history		
	Acute exacerbations of the disease	
	Sometimes fixed airflow limitation, even in non-smokers	Usually progressive, sometimes accelerated, FEV1 decline
severe chronic respiratory failure	Absent in non-smokers	Main cause of chronic respiratory failure necessitating long-term oxygen therapy
lung cancer risk	Not increased in non-smokers	Increased compared to age/smoke-history matched smokers with normal lung function
pulmonary emphysema risk	Not increased in non-smokers	Associated with advanced disease
Common co-morbidities		
	Allergy, rhinosinusitis	Chronic heart failure, diabetes mellitus, atherosclerosis-associated diseases
Mortality rate over general population	Slightly increased	Greatly increased
Triggers for exacerbations		
	Aeroallergens	
	Viral respiratory infections	Bacterial and viral respiratory infections
	Tobacco Smoke	
	Air pollution	
	Extremes in temperature: cold-wet/hot	
	Physical activity	
	Drugs administration or withdrawal	

Table 3. Current therapeutics for Asthma/COPD: approved biologicals and SMD

	Biologicals					
	Target	**Drug name**	**Indications**	**Molecule type**	**Discontinued**	**Approved***
	Soluble					
	IgE	Omalizumab	asthma	antibody		FDA/EMA
	IL-5	Mepolizumab	asthma	antibody		FDA/EMA
		Reslizumab	asthma	antibody		FDA/EMA
	Membrane-bound					
	IL-5Ra	Benralizumab	asthma	antibody		FDA/EMA
	SMDs					
	Membrane-bound					
LTRAs	CYSLTR1, CysLT1 receptor					
		Montelukast	asthma	antagonist		FDA
		Zafirlukast	asthma	antagonist		FDA/EMA
SABAs	ADRB2	Fenoterol	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Levalbuterol	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Salbutamol (albuterol)	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
LABAs		Arformoterol	COPD	agonist		FDA/EMA
		Formoterol	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Olodaterol	COPD	agonist		FDA/EMA
		Salmeterol	asthma	agonist		FDA/EMA
			COPD	agonist	yes	FDA/EMA
ULABAs		Indacaterol	asthma	agonist		FDA/EMA
		Vilanterol	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
SAMAs	Inhaled muscarinic receptors antagonists					
		Ipratropium bromide	COPD	antagonist		FDA
LAMAs		Umeclidinium	COPD	antagonist		FDA/EMA
		Aclidinium	COPD	antagonist		FDA/EMA
ULAMAs		Glycopyrronium	COPD	antagonist		FDA/EMA
		Tiotropium	asthma	antagonist		FDA/EMA
			COPD	antagonist		FDA/EMA
	PDE4	Ibudilast	asthma	inhibitor		FDA/EMA
		Roflumilast	COPD	inhibitor		FDA/EMA
	Intracellular / nuclear					
	5-lipoxygenase / ALOX5	Zileuton	asthma	inhibitor		FDA
Inhaled Corticosteroids (ICS)	Glucocorticoid receptor (GR) / *NR3C1*	Beclomethasone dipropionate	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Budesonide	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Ciclesonide	asthma	agonist		FDA/EMA
		Fluticasone propionate/furoate	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Mometasone furoate	asthma	agonist		FDA/EMA
Systemic CS		Betamethasone	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Deflazacort	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Hydrocortisone	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Methylprednisolone	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
		Prednisone	asthma	agonist		FDA/EMA
			COPD	agonist		FDA/EMA
	Mast cell stabilizers					
		Cromolyn sodium	asthma	inhibitor	yes	FDA
	* only EMA/FDA currently approved compounds listed					

Table 4. Comparison of SMDs and biologicals.

	SMDs	Biologicals
Molecular weight (kDa)	less than 1	44-150
Structure	Chemical compounds	Immunoglobulins, enzymes, recombinant proteins
Manufacturing	Chemical synthesis, highly reproducible	Living organisms, sensitive to minor changes
Active principle	Unique, well defined	Mix of slightly heterogenous proteins and impurities
Dosing route	Inhalation, oral, intramuscular (rare), intravenous (mostly in emergency)	subcutaneous, intravenous
Dose interval	hours-1 day (occasional for on needs drugs)	1-4 weeks
Distribution	Dependent on the chemical properties of the drug	Target-dependent
Blood-brain barrier permeability	Possible	No
Half life	Hours-some days	Weeks
Metabolism/degradation	Hepatic (metabolism by cytochromes and non-microsomal enzymes)	Proteolytic degradation in the tissues, opsonization by monocyte/macrophage system (lysosomal degradation), endocytosis by target cells
Excretion	Renal	No excretion
Target	Extracellular, cytoplasmic, nuclear	Extracellular
Specificity	Low, medium, high, very high	Very high
Immunogenicity	Rare	Possible

Table 5. Biologicals under clinical investigation for Asthma/COPD: current status

Biologicals					
Target	**Drug name**	**Indications**	**MoleculeType**	**Discontinued**	**Study Phase**
Soluble					
IgE	MEDI4212	asthma	antibody	yes	Phase 1
	Ligelizumab / QGE031	asthma	antibody		Phase 2
IL-1b	Canakinumab	COPD	antibody	yes	Phase 2
IL-4	Altrakincept	asthma	rec. IL4R	yes	Phase 1
	Pascolizumab	asthma	antibody		Phase 2
	VAK694	asthma	antibody		Phase 2
IL-4/IL-13	QBX258 (VAK-694/QAX-576)	asthma	antibody		Phase 2
IL-5	Mepolizumab	COPD	antibody		Phase 3
IL-9	Enokizumab	asthma	antibody	yes	Phase 2
IL-8	ABX-IL8	COPD	antibody	yes	Phase 2
IL-13	ABT-308	asthma	antibody	yes	Phase 1
	Anrukinzumab	asthma	antibody	yes	Phase 2
	CNTO 5825	asthma	antibody		Phase 1
	Dectrekumab (QAX576)	asthma	antibody		Phase 2
	GSK679586	asthma	antibody	yes	Phase 2
	Lebrikizumab	asthma	antibody	yes	Phase 3
		COPD	antibody	yes	Phase 2
	IMA-026	asthma	antibody		Phase 1
	Tralokinumab	asthma	antibody	yes	Phase 3
		COPD	antibody	yes	Phase 3
IL-17A	Secukinumab	asthma	antibody	yes	Phase 2
IL-13 / IL-17A	RG7990	asthma	antibody		Phase 1
TNF	Golimumab	asthma	antibody	yes	Phase 2
	Infliximab	asthma	antibody		Phase 2
		COPD	antibody		Phase 3
	Etanercept	asthma	protein inhibitor	yes	Phase 2
		COPD	protein inhibitor		Phase 2
GMCSF / CSF2	Lenzilumab / KB003	asthma	antibody	yes	Phase 2
OX40L / TNFSF4	Oxelumab / huMab OX40L	asthma	antibody	yes	Phase 2
Neutrophil elastase	Zemaira	COPD	protein inhibitor		Phase 4
	Aralast	COPD	protein inhibitor		Phase 4
	Glassia	COPD	protein inhibitor		Phase 4
TSLP	Tezepelumab	asthma	antibody		Phase 3
Membrane-bound					
IL-1R1	MEDI8968	COPD	antibody	yes	Phase 2
IL-2R / CD25	Daclizumab	asthma	antibody	yes	Phase 2
IL4Ra	Dupilumab	asthma	antibody		Phase 3
	Pitrakinra	asthma	antibody	yes	Phase 2
IL-5Ra	Benralizumab	COPD	antibody	yes	Phase 3
IL-17AR	Brodalumab	asthma	antibody	yes	Phase 2
	RG7258	asthma	antibody	yes	Phase 1
CXCR2	MK-7123	asthma	antibody		Phase 2
Siglec-8	AK001	asthma	antibody	yes	Phase 2

Table 6. SMDs under clinical investigation for Asthma/COPD: current status

SMDs					
Target	**Drug name**	**Indications**	**MoleculeType**	**Discontinued**	**Study Phase**
Soluble					
MMP-9 /12	AZD1236	COPD	inhibitor	yes	Phase 2
Membrane-bound					
IL4Ra	AIR645	asthma	antisense oligo		Phase 2
IL8R/CXCR2	Navarixin / MK-7123	asthma	antagonist		Phase 2
		COPD	antagonist	yes	Phase 2
	AZD5069	asthma	antagonist		Phase 2
		COPD	antagonist		Phase 2
CCR2b	AZD2423	COPD	antagonist	yes	Phase 2
CYSLTR1	Pranlukast	asthma	antagonist		Phase 3
	Zafilukast	asthma	antagonist		Phase 3
CRTH2/ PTGD2R	Fevipiprant / QAW039	asthma	antagonist		Phase 3
	Timapiprant /OC000459	asthma	antagonist		Phase 3
	AZD1981	asthma	antagonist		Phase 2
		COPD	antagonist		Phase 2
	ACT-129968/ KYTH-105/ setipiprant	asthma	antagonist	yes	Phase 2
	RG7185	asthma	antagonist	yes	Phase 1
TBXA2R	Seratrodast	asthma	antagonist	yes	Phase 3
		COPD	antagonist	yes	Phase 3
Muscarinic receptors	Umeclidinium	asthma	antagonist		Phase 3
	Glycopyrronium	asthma	antagonist		Phase 4
Histamine receptors	JNJ-39758979	asthma	H4 antagonist	yes	Phase 2
	JNJ-38518168/Toreforant	asthma	H4 antagonist	yes	Phase 2
PDE3/4	RPL554	asthma	inhibitor		Phase 2
		COPD	inhibitor		Phase 2
PDE4	Roflumilast	asthma	inhibitor	yes	Phase 3
	Ciomilast	asthma	inhibitor	yes	Phase 1
c-KIT, PDGFRA and PDGFRB	Imatinib	asthma	inhibitor		Phase 2
Intracellular / nuclear					
5-lipoxygenase / ALOX5	Zileuton	COPD	inhibitor	yes	Phase 3
	MK-0633 / Setileuton	asthma	inhibitor	yes	Phase 2
		COPD	inhibitor	yes	Phase 2
	PF-04191834	asthma	inhibitor	yes	Phase 2
Glucocorticoid receptor (GR)/*NR3C1*	Triamcinolone acetonide	asthma	agonist		Phase 2
		COPD	agonist		Phase 3
	Mometasone furoate	COPD	agonist		Phase 3
PI3K/p110d	Nemiralisib/GSK2269557	asthma	inhibitor		Phase 2
		COPD	inhibitor		Phase 2
pan-JAK (JAK1, 2, 3 and Tyk2)	VR588	asthma	inhibitor		early Phase 1
MAPKs	Simvastatin	asthma	p38 inhibitor	yes	Phase 3
		COPD	p38 inhibitor	yes	Phase 3
	AZD7624	COPD	p38 inhibitor	yes	Phase 2
	PF-03715455	asthma	p38 inhibitor	yes	Phase 1
	CHF6297	COPD	p38α inhibitor	yes	Phase 1
	SB681323	COPD	p38 inhibitor	yes	Phase 1
	PF03715455	COPD	p38 inhibitor	yes	Phase 2
	Losmapimod	COPD	p38 inhibitor	yes	Phase 2
GATA-3	SB010	asthma	DNAzyme		Phase 1/2
Mast cell stabilizer					
	Nedocromil	asthma	inhibitor		Phase 3

Table 7. Biologicals and SMDs in asthma and COPD: Common critical points, unmet needs and potential gains from integrated therapeutical strategies.

· **Right target**
- Target identification in highly heterogenous clinical entities: non-T2 and neutrophilic asthma, COPD
- Better deconvolution of human kinome for SMDs
- Identification of targets useful across multiple disease phenotypes
- Combining intracellular and extracellular targeting: mechanisms of synergy
· **Right safety**
- Target liability, pharmacokinetics, pharmacodynamics, genotoxicity
- Optimized pharmacology to avoid off-target activities
- Drug-drug interactions in drug combination strategies
- Long-term safety risks of blocking pathways (e. g. anti-eosinophil drugs)
· **Right patient**
- Defining responsive patients
- Complexity of adequate biomarker identification: include multi-omics stratification tools
- Biomarkers for SMDs: extend search and validation beyond those used for stratifications in trials with biologicals
· **Right treatment**
- Explore adequate targeted treatment algorithms and treatment duration
- Assess long-term targeted treatment effects and the risk of relapse on withdrawal
- Safe and effective targeted treatments in vulnerable patient populations: i.e., children, pregnancy, elderly
- Therapeutic potential of SMDs combinations and combinations of SMDs and biologicals
· **Right economic considerations**
- Biologicals' high cost restrict their usage; alternatively, cost reduction may arise by reducing long-term disease risks and complications
- Cost reduction by combined biological/SMD therapy through dose-sparing effects
- Cost reduction by reversal of glucocorticoid resistance through SMDs
- Cost effectiveness calculated as the sum of immediate and long-term risk reductions

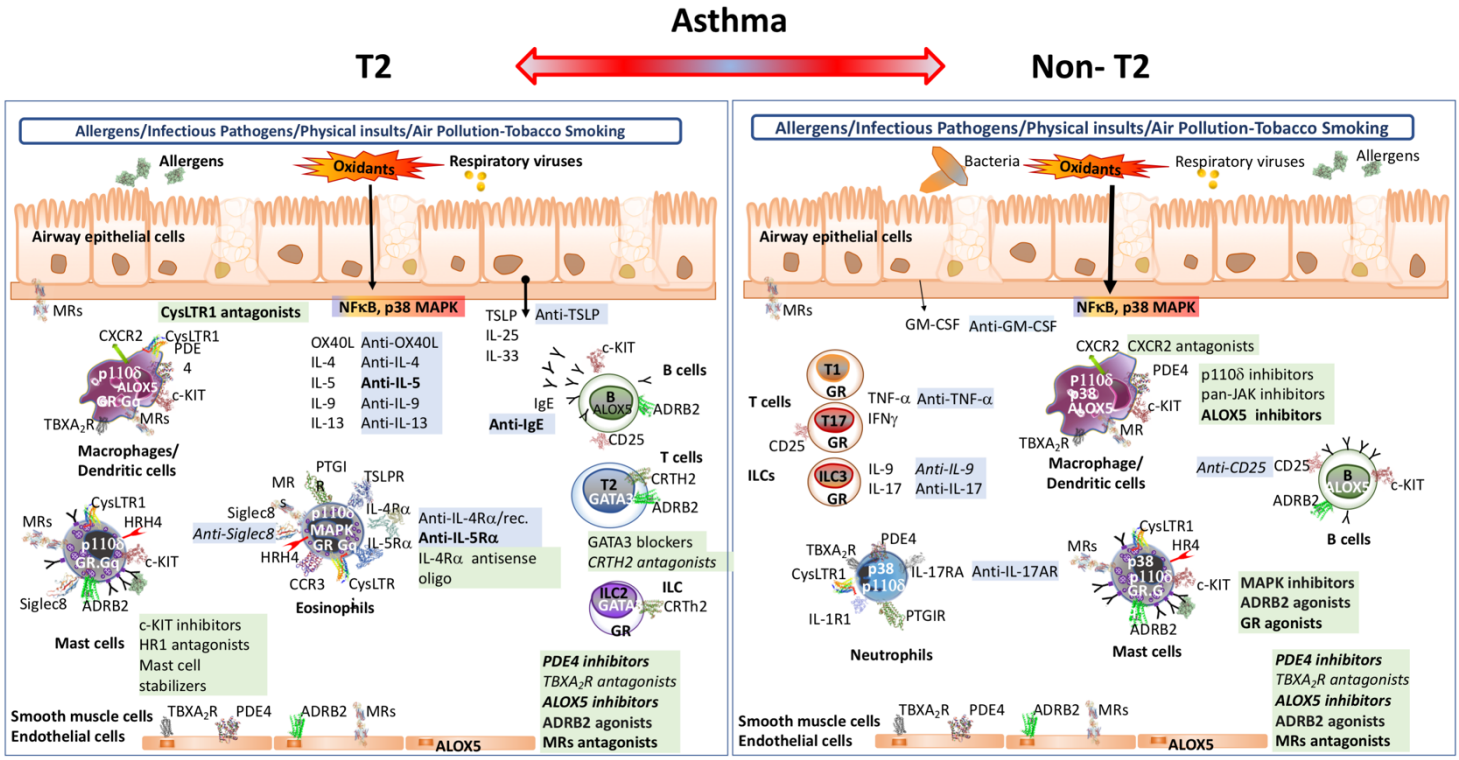
Figure Legends

Figure 1. Current drug strategies with biologicals and SMDs for T2/non-T2 Asthma.

Standard therapy for asthma includes the use of glucocorticoids (GR activation), drugs targeting the adrenergic receptor ADRB2 and inhibiting the synthesis (ALOX5) of function (CysLTR1) of leukotrienes. **Left Panel (T2)**. For asthma associated with atopy and refractory, hypereosinophilic asthma: anti-IgE and anti-IL-5 treatment are currently approved (all biologicals in blue boxes); also targeted are T2-associated cytokines (such as TSLP, IL-4, IL-5, OX40L, IL-9, IL-13), their receptors (IL-4Rα, IL-5Rα, TSLPR) or receptors implicated in Th2/ILC2 cell recruitment such as CRTh2 (see Section 2). Other SMD-based strategies (green boxes) target mast cells either by blocking the receptor for survival factor kit, or by impeding its activation by antagonizing histamine receptors, or by using mast cell granule-stabilizing agents. **Right Panel (Non-T2)**. For non-T2 or neutrophilic asthma, treatment strategies with biologicals under investigation have targeted inflammatory cytokines such as IL-17 and its respective receptor, or TNFα. Biologicals also aim at blocking the recruitment of neutrophils either by inhibiting CXCL8 or its receptor or inhibiting neutrophilic proliferation targeting GM-CSF. The production of IFNγ is targeted with SMD p120.

Figure 2. Current drug strategies with biologicals and SMDs for COPD. Chronic exposure to pollutants, particularly deriving from tobacco smoke, causes the formation of oxidants [reactive nitrogen and oxygen species (RNS/ROS)] and triggers chronic inflammatory responses of the airway epithelial cells and lung macrophages to inhaled irritants. Approved treatments for COPD include - dependent on severity - bronchodilators acting on the adrenergic receptor (ADRB2) such as SABA or LABA, or on muscarinic receptors (MRs), drugs impeding leukotriene function (CysLTR1) or inhibiting elastase released from neutrophils. Glucocorticoids have limited indication, mainly following exacerbations. Under clinical investigations are drugs impeding monocytic (CCR2) or neutrophil recruitment by blocking IL-8 or its receptor (CXCR2), blocking inflammatory cytokines such as TNFα or IL-1 and its receptor (IL1R) synthesis, inhibiting proteases (MMP-9/12) released by neutrophils and macrophages and inhibiting phosphoinositide 3-kinase (PI3K) delta isoform p110δ, an enzyme critical for the activation of T cells, B cells, mast cells and neutrophils. Anti-IL5, anti-IL-13 and anti-IL-5Rα antibodies have been evaluated in eosinophilic COPD.

Figure 1



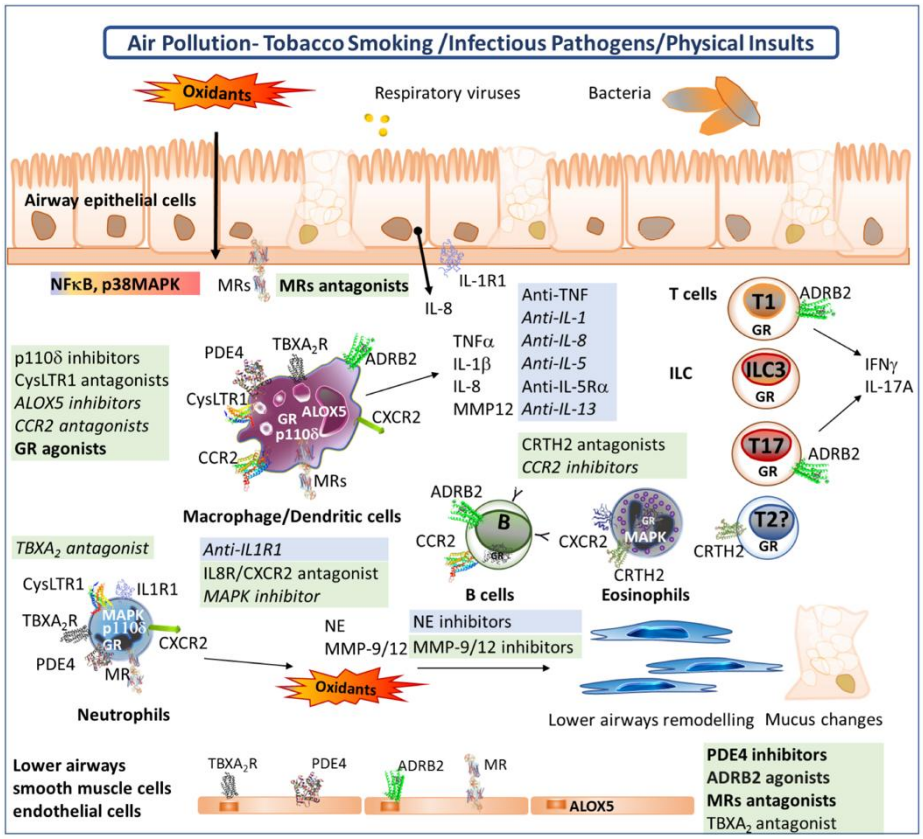
approved drugs, drugs in clinical trials, *trials discontinued*

SMDs

Biologicals

ADRB2: β2–adrenoreceptor, ALOX5: 5-lipoxygenase, c-KIT: CD117/stem cell growth factor receptor/ tyrosine-protein kinase, CRTH2: Chemoattractant receptor-homologous molecule expressed on TH2 cells, CysLTR1: Cysteinyl leukotriene receptor 1, CXCR2: interleukin 8 receptor, Gq: guanine nucleotide-binding G protein subunit, GR: glucocorticoid receptor, HR1: histamine receptor 1, IgE: immunoglobulin E, MRs: muscarinic receptors, PDE4: phosphodiesterase 4, p110δ: phosphoinositide 3-kinasePI3K delta, PTGIR: Prostaglandin I2 Receptor, $TBXA_2R$: thromboxane receptor

Figure 2



ADRB2: β–adrenoreceptor, ALOX5: 5-lipoxygenase, CRTH2 : Chemoattractant receptor-homologous molecule expressed on TH2 cells, CysLTR1: cysteinyl leukotriene receptor 1, CXCR2: Interleukin 8 receptor, Gq: Guanine nucleotide-binding G protein subunit, GR: Glucocorticoid receptor, c-KIT: CD117/stem cell growth factor receptor/ tyrosine-protein kinase, MR: muscarinic receptor, NE: neutrophil elastase, PDE4: phosphodiesterase 4, p110δ: phosphoinositide 3-kinasePI3K delta, $TBXA_2R$: thromboxane receptor

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METHODS

A systematic review of the literature was performed in PubMed and by search of the databases such as European clinical trials database, EudraCT and ClinicalTrials.gov. Moreover, biologicals and SMD were searched via the database of the International Union of Basic and Clinical Pharmacology, IUPHAR, and the British Pharmacological Society, BPS(10) using COPD and asthma as keywords.

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