Current and future developments in the pharmacology of asthma and COPD: ERS seminar, Naples 2022

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Shareable abstract (@ERSpublications)
European pneumologists and pharmacologists review the pharmacology of drugs currently used to treat asthma and COPD and the challenges for novel drugs based on precision medicine, tissue remodelling and regeneration, pharmacogenomics and biosimilars https://bit.ly/42h55HS

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Abstract

Pharmacological management of airway obstructive diseases is a fast-evolving field. Several advances in unravelling disease mechanisms as well as intracellular and molecular pathways of drug action have been accomplished. While the clinical translation and implementation of *in vitro* results to the bedside remains challenging, advances in comprehending the mechanisms of respiratory medication are expected to assist clinicians and scientists in identifying meaningful read-outs and designing clinical studies. This European Respiratory Society Research Seminar, held in Naples, Italy, 5–6 May 2022, focused on current and future developments of the drugs used to treat asthma and COPD; on mechanisms of drug action, steroid resistance, comorbidities and drug interactions; on prognostic and therapeutic biomarkers; on developing novel drug targets based on tissue remodelling and regeneration; and on pharmacogenomics and emerging biosimilars. Related European Medicines Agency regulations are also discussed, as well as the seminar's position on the above aspects.

Pharmacology of asthma and COPD: current knowledge

Understanding the nature and mechanism of action of the current pharmacological therapy of bronchodilators in asthma and COPD (Maria Gabriella Matera)

Inhaled bronchodilators (antimuscarinics and β_2-agonists) are critical to the optimal management of patients with COPD at all phases of the disease (https://goldcopd.org/) and are crucial in the management of patients with asthma (https://ginasthma.org). The rationale for using bronchodilators lies in the ability of the drugs to interfere with the mechanisms of broncho-motor tone control in the airway smooth muscle (ASM) [1].

Inhaled antimuscarinics (these can be short-acting (SAMA), but are mainly long-acting (LAMA)) act as non-selective antagonists of muscarinic receptors (MR) on ASM and mucous glands in the bronchial tree following stimulation of the parasympathetic vagal nerves (at ganglia and neuroeffector junction). LAMA include tiotropium, which binds to all three MR subtypes, with very slow dissociation from the M_3 and rapid dissociation from the M_2 subtype in airways; and the newer drugs, glycopyrronium, umeclidinium and aclidinium, that exhibit good selectivity for and slow dissociation from the M_3 MR [1–3].

β_2-adrenoceptors (AR) are abundantly expressed in human ASM, even though they have scarcely any direct adrenergic innervation [1]. β_2-agonists activate adenylyl cyclase (AC) to produce cAMP that leads to relaxation of ASM through sequestration of intracellular Ca^{2+} [1, 4]. cAMP also activates exchange factor directly activated by cAMP (Epac) and cAMP-dependent protein kinase A (PKA). The former downregulates Rho and leads to relaxation of ASM; the latter controls the tone of ASM *via* phosphorylation of key regulatory proteins [4]. It is evident, however, that relaxation of ASM through AC-coupled pathways is substantially more complex and the precise signalling pathways remain to be clarified [1, 4, 5].

Short-acting β_2-agonists (SABA; 4–6 h, *e.g.* albuterol/salbutamol, metaproterenol, and terbutaline), long-acting β_2-agonists (LABA; 12 h, *e.g.* clenbuterol, formoterol and salmeterol) and ultra-LABA (U-LABA; 24 h, *e.g.* abediterol, carmoterol, indacaterol, olodaterol and vilanterol) are all highly selective for the β_2-AR, but they differ in terms of intrinsic efficacy [1]. Formoterol and isoprenaline, full agonists of β_2-AR, cause almost a complete relaxation at higher doses, while partial agonists, such as salmeterol, indacaterol, olodaterol and vilanterol, can induce only 70% of maximal relaxation at higher doses [1, 6]. Clinically, in a phase of remission, a full and a partial agonist induce the same bronchorelaxant effects due to the large reserve of AR in the lung. However, during an exacerbation, the response of a partial agonist may be less effective because of β_2-AR heterologous desensitisation induced by inflammatory mediators [1, 6–8].

Both LAMA and LABA are key agents in the treatment of asthma and COPD because they alleviate bronchial obstruction and airflow limitation, reduce hyperinflation, and improve emptying of the lung and exercise performance [1]. Current guidelines recommend treatment that combines a LAMA with a LABA, rather than increasing the dose of either as monotherapy, in patients complaining of dyspnoea or exercise intolerance. The combination of a drug that blocks M_3 MR and another that activates β_2-AR shifts the relaxation/contraction imbalance of ASM towards a relaxed profile, which is essential in patients with chronic airway obstruction [1, 4, 5, 9].

The effectiveness of dual pharmacological intervention for bronchodilation involves complex adrenergic and cholinergic systems mechanisms [1]. At the post-junctional level, this is mainly achieved by the activation of β_2-AR and the blockade of M_3 MR [2]. At that level, the extent of ASM relaxation is also influenced by a direct interaction between M_3 MR and β_2-AR, as follows: the production of inositol triphosphate that is mediated following activation of the M_3 MR by acetylcholine may be limited, probably due to the activation of PKA induced by β_2-AR agonists, thus decreasing intracellular Ca^{2+} and, therefore, the contraction of ASM. On the other hand, antagonists of M_3 MR prevent the phosphorylation and, consequently, the desensitisation of β_2-AR and/or Gs proteins, which occurs through activation of protein kinase C following stimulation of M_3 MR by acetylcholine [2]. At the pre-junctional level, activation of β_2-AR decreases acetylcholine release into synapses through modulation of cholinergic neurotransmission that involves Ca^{2+}-activated K^+ channels. This leads to an amplification of ASM relaxation induced by the blockade of post-junctional M_3 MR. Thus, an antagonist of the M_3 MR will operate in a more favourable context due to a β_2-agonist induced reduction in acetylcholine release. Accordingly, the effect on the ASM caused by an agonist on the β_2-AR will also be amplified [1, 9–11].

The available evidence for the currently approved drugs indicates that the combination of LABA and LAMA is an effective approach to optimise bronchodilation. These combinations provide established benefits for patients suffering from asthma or COPD, either for short- or long-term treatments, and reduce the need for increasing the dose of the monocomponents and thus the risk of adverse events.

The mechanisms by which inhaled corticosteroids interact in COPD (Maarten van den Berge)

Inhaled corticosteroids (ICS) may have beneficial effects in a subset of COPD patients. It has been recommended to initiate or continue ICS treatment in combination with LABA/LAMA in COPD patients with a history of recurrent or severe exacerbations, a history of concomitant asthma, or in those with blood eosinophil levels >300 cells·μL^{-1} [12, 13]. Blood eosinophil counts predict ICS treatment response in COPD, but are not a perfect biomarker [14].

RNA-sequencing may help to better predict corticosteroid treatment responsiveness. Using genome-wide gene expression profiling in the SYMBEXCO trial, nine genes were identified that are differentially expressed in COPD patients who developed an early exacerbation after ICS withdrawal. When compared to a model using eosinophils from sputum, the addition of an unbiased gene signature to a multiple Cox regression explained more variance in time to exacerbations. These data indicate that patients who are at higher risk of exacerbation after ICS withdrawal can be identified by gene expression in sputum [15–18]. Several genes included in this signature, such as *IL1RL1, LGALS12, EMR4P* and *CLC*, have already been identified to be involved in airway type 2 eosinophilic inflammation [15]. However, other pathways of interest were also identified in the signature including mast cell and macrophage-related inflammatory genes (*IL1RL1, ALOX15*), and genes related to cluster of differentiation 4 ($CD4^+$) (*CLC*) and $CD8^+$ T-cell differentiation (*IL1RL1, CD24*) [15].

To identify genes that are ICS sensitive, a mass screen of bronchial biopsies pre- and post-ICS treatment was performed. Across all studies, FK506 binding protein 5 (FKBP5) [19] was found to be the most significantly upregulated by ICS treatment (as yet, unpublished data from Maarten van den Berge; personal communication). This gene is known to bind to the immunosuppressants FK506 and rapamycin indicating a potential role in inflammation. Subsequent knockout studies of FKBP5 in the epithelial cell line A549, showed that cells lacking this gene were six times more sensitive to ICS and additionally had a blunted response to inflammatory stimuli such as tumour necrosis factor α (TNF-α), which was found to act through nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF-κB) [20]. Recently, a specific FKBP5 inhibitor SAFit1 passed stage 1 clinical trials as a treatment for depression [21]. Repurposing this drug as an anti-inflammatory treatment for difficult to treat chronic inflammatory diseases would greatly improve ICS sensitivity in these patients.

In conclusion, ICS may have beneficial effects in a subset of COPD patients. Blood eosinophil counts predict ICS treatment response in COPD, but are not a perfect biomarker. RNA-sequencing may help to better predict corticosteroid treatment responsiveness, but this needs to be confirmed in future studies. FKBP5 is one of the genes most upregulated by corticosteroids, this may represent a negative feedback loop as increased FKBP5 expression counteracts the effects of ICS. Inhibiting this negative feedback loop may represent a way to improve corticosteroid insensitivity in COPD.

Biomarker-guided pharmacological intervention in COPD (Daiana Stolz)

Disease-specific biomarkers can be used as tools for evidence-based care and for precision medicine to adjust treatment to individuals or subgroups of patients [21, 22]. Disease-specific biomarkers can be predictive biomarkers, *i.e.* predict those that will benefit and those who will only experience harm from therapeutics; therapeutic biomarkers (or response biomarkers), *i.e.* predict response to a certain drug at individual level; and prognostic biomarkers, *i.e.* can be used to segregate patients at risk of poor outcome from those with stable disease [23].

Disease-specific biomarkers include, among others, molecules that reflect extracellular matrix turnover, such as matrix metalloproteinases, glycosaminoglycans and collagens, and their degradation products. These biomarkers have been associated with disease severity and disease outcome in COPD [24–26].

Theragnostic biomarkers have also been used in the field of theragnostics, which is the treatment strategy that combines therapeutics with diagnostics and associates both a diagnostic test that identifies the patients most likely to be helped or harmed by a new medication, and targeted drug therapy based on the test results [27, 28].

In COPD, diagnostic biomarkers include forced expiratory volume in 1 s (FEV_1)/ forced vital capacity (FVC), computed tomography (CT) scan and diffusion capacity; prognostic biomarkers include the BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) score and pulmonary hypertension; therapeutic biomarkers in the stable state include arterial oxygen tension, emphysema morphology and eosinophils, and at exacerbation they include procalcitonin, C-reactive protein (CRP), blood eosinophils and sputum colour; a response biomarker is serum alpha-1 antitrypsin level [23, 29–32].

Disease-specific biomarkers have also been used to withhold therapy. For example, blood eosinophils have been used to withhold therapy with steroids and procalcitonin and CRP for the use of antibiotics. Exhaled nitric oxide fraction (F_{ENO}) can be used to predict ICS response at upper respiratory tract infection (URTI) and the probability of an acute exacerbation of COPD [33–38].

In conclusion, there is a great necessity for discovering superior biomarkers to the existing ones for COPD. Novel biomarkers must improve patient management and outcomes, must be economical, with a nominal

cost or must cause downstream healthcare savings, and must have convenient to use analytical technology to be implemented in a clinical laboratory. Biomarker-guided pharmacological intervention for COPD therapy is essential to guide the clinical care of individuals with COPD and to enhance the possibilities of success in drug development. In this respect, a panel of disease-specific biomarkers may be more efficient than a single biomarker for a more detailed understanding of the clinical and biological heterogeneity of COPD that would lead to personalised medicine.

Emerging new concepts and treatments

Do we understand remodelling in asthma and COPD? (Eleni Papakonstantinou)

Despite the great advances in the field in recent years, airway remodelling remains one of the most intractable problems in chronic lung diseases, leading to irreversible loss of lung function. In asthma and COPD airway remodelling refers to the structural aberrations from healthy lung, and includes hyperplasia of epithelial cells, metaplasia and hyperplasia of squamous cells, thickening of reticular basement membrane, deposition of extracellular matrix molecules such as collagen, and angiogenesis [39, 40].

However, significant differences also exist in airway remodelling between asthma and COPD. In large airways of patients with mild stable COPD an elevated number of $CD8^+$ T-cells, neutrophils and macrophages have been observed, whereas in patients with mild stable asthma increased numbers of $CD4^+$ T-cells, eosinophils and mast cells have been reported. Remodelling also occurs in small (<2 mm) airways of patients with asthma or COPD [41]. However, this compartment is difficult to access. Eosinophils, T-cells and mast cells are prominent in asthma small airways, whereas in COPD there are mainly neutrophils, T-cells, B-cells and macrophages. In this respect, specific histopathological findings reflecting airway remodelling, such as thickening of basement membrane in COPD patients, may reveal an overlapping COPD–asthma phenotype [41–43].

Airway remodelling has a high clinical impact and, therefore, its assessment is of great relevance. In this respect, caution should be taken, as there are significant differences in features of airway remodelling between different lung lobes [44–46]. Today, CT is a remarkable tool to assess airway wall morphology *in vivo* since sub-millimetric acquisitions over the whole lung volume can be obtained allowing three-dimensional evaluation [45].

Circulating biomarkers, such as proforms of collagens, collagen fragments, matrix metalloproteinase and fragments of hyaluronic acid can also be used as indices of airway remodelling [24–26, 46–48].

Airway remodelling can be targeted by pharmacological treatment with glucocorticoids, β_2-agonists, leukotriene inhibitors and novel treatments with biological agents [49]. Recently, hyaluronic acid and its degrading enzyme hyaluronidase-1 have been shown to be promising as potential targets to control inflammation and airway remodelling in COPD patients [50, 51]. Bronchial thermoplasty is a non-pharmacological treatment targeting airway remodelling in severe asthma. It applies selective heating of 65°C for 10 s at selected structural components of the airways, aiming to improve asthma symptoms [52, 53]. Early pharmacological and non-pharmacological interventions to prevent airway remodelling will undoubtedly help to intercept the development of asthma and COPD, but much remains to be studied about this possibility.

Lung regeneration in COPD: is it still far from reality? (Reinoud Gosens)

COPD is characterised by a progressive loss of lung function and airflow limitation that is not fully reversible. The key problem underlying COPD pathogenesis is abnormal tissue repair, causing bronchitis and small airways remodelling on one hand and emphysema on the other [54]. Current approaches to COPD focus on prevention of further lung damage (tobacco control and environmental air pollution legislation) and symptomatic treatment of infective exacerbations, including lung volume reduction, in selected patients.

As current pharmacological or non-pharmacological treatments do not modify the course of the disease, new therapies need to be developed. Unless the abnormal interplay between inflammatory and repair processes can be halted or reversed, the outlook for patients with COPD remains poor and most patients will remain on non-curative treatment for the rest of their lives. The major hurdle that obstructs the development of new therapies is the immense lack of knowledge on the mechanisms that impair adequate tissue repair in COPD. A hypothesis put forward is that the diseased local tissue microenvironment is the key driver of impaired tissue repair in COPD and that it should be feasible to reactivate lung repair with regenerative therapy pharmacologically targeting the microenvironment [55].

Lung repair or regeneration strategies, which have the more ambitious aim of reversal of established lung disease, are a potentially high return, long-term research goal that may provide a novel approach for patients with COPD whose major pathology is a lack of functioning lung tissue [55]. Regenerative medicine for the emphysematous lung has, thus far, mainly focused on either tissue engineering approaches following surgical interventions, on stem or progenitor cell therapy, or a combination of these. Tissue engineering is highly appropriate to reconstruct the damaged lung in end-stage disease, where endogenous reactivation of repair is going to be futile. However, this approach does have several limitations that will need to be addressed [56–61].

Pharmacological targeting may aid or support regenerative strategies involving stem cells. However, a major hurdle in developing such a pharmacological approach is the immense lack of knowledge on the intricate regulatory mechanisms underlying impaired tissue repair in COPD. Although it is clear that tissue repair is prevented by a hostile microenvironment in COPD, the precise mechanisms involved and druggability of these targets are at present largely unknown. Without the knowledge of these mechanisms, appropriate reactivation cannot be achieved.

According to this hypothesis, pharmacological targeting should be feasible to reactivate lung repair. This may involve maintenance treatment with pathway modifiers to support repair, or specific treatment during disease exacerbations, which are key periods of accelerated lung function decline in COPD, representing windows of opportunity for more unconventional therapeutic strategies. According to already published data, stem cell therapy and organoid therapy represent potential ways forward in achieving lung repair, provided that technical hurdles are overcome to improve efficacy. Activation of wingless-related integration-a site and niche cell derived extracellular vesicles enhances initial cell division of epithelial progenitors and supports organoid growth [62, 63]. Multiple inflammatory cytokines and cigarette smoke repress adult epithelial lung organoid formation. Prostaglandins E2 and I2 are potential drug targets for lung repair, preventing these negative interactions [64].

Emerging classes of drugs for the treatment of obstructive lung disease (Dave Singh)

The development of novel therapies for asthma and COPD requires a precision medicine approach, using both clinical information (clinical phenotype) and biological markers (endotypes) in order to identify subgroups with the greatest potential for therapeutic benefit [65]. Drugs with novel mechanisms of action are being developed for airway diseases, the most promising new drug classes with identification of responder subgroups are discussed in the following paragraphs.

Biological treatments targeting alarmin cytokines have shown positive clinical trial results in both asthma and COPD. The airway epithelium senses external danger signals to initiate host innate immune defence mechanisms by the rapid secretion of alarmins, including thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33). These alarmins are capable of initiating both type-2 (T2) and non-T2 immune responses. Tezepelumab is a monoclonal antibody directed against TSLP, which has shown clinical efficacy, including exacerbation rate reduction, in large clinical trials across the range of T2-high and T2-low severe asthma patients, although the effect appears to be greater in the T2-high population [66–68]. The optimal positioning of this biological treatment in the severe asthma population in relation to existing anti-T2 biologics has yet to be defined [68].

Biological treatments targeting the IL-33 pathway have shown clinical efficacy in phase 2 asthma and COPD studies. The efficacy of itepekimab (which targets IL-33) on exacerbation rate reduction in COPD patients appeared to be greater in ex-smokers than current smokers [69, 70]. This finding, if confirmed, may lead to biological treatment in COPD that is confined to ex-smokers.

Questions remaining for the use of anti-alarmin treatments include the magnitude of benefit of anti-IL-33 in asthma, the group of asthma patients to be targeted, the use of anti-IL-33 treatment in COPD, and whether should it target ex-smokers only. Also, the role of anti-TSLP in COPD remains to be clarified [71, 72].

Kinases control intracellular signal transduction, generating a cellular response to external signals through the phosphorylation of proteins and lipids, causing functional changes that result in enzyme activation or translocation. Kinases can control multiple intracellular signal transduction cascades involved in inflammation. Drugs targeting kinases (*e.g.* baricitinib, tofacitinib, upadacitinib) offer potential for broad anti-inflammatory effects, but kinase cross-talk means that other overlapping kinases may limit the effectiveness of selective kinase-targeting approaches to drug development [73–76]. Furthermore, the widespread expression of kinases in different cell types and tissues enhances the possibility of adverse

effects. Besides safety, unresolved questions for the use of Janus kinase (JAK) inhibitors in asthma include the magnitude of clinical benefit and the effect on non-T2 inflammation in asthma [74–76].

Ensifentrine is an inhibitor of both the phosphodiesterase (PDE)3 and PDE4 isoforms [77]. PDE3 controls smooth muscle tone; PDE3 inhibition causes bronchodilation and also has some anti-inflammatory effects. PDE4 inhibition has the potential to exert broad anti-inflammatory effects. Ensifentrine has demonstrated bronchodilation and symptom improvement in COPD clinical trials and has the possibility to be the first novel bronchodilator to be successfully developed for decades [65, 77].

Challenges in the treatment of patients with asthma and COPD

New insights into steroid resistance (Nicola Hanania)

Corticosteroids induce resistance in asthma and COPD patients [78]. 5–10% of the asthmatic population responds poorly to high doses, and 1% requires systemic corticosteroids [79]. These patients form a category of severe asthma associated with poor quality of life and increased morbidity and mortality, and constitute a major societal and health burden. In patients with COPD, most are resistant to inhaled or oral corticosteroids, indicating steroid resistance of the underlying inflammatory response.

There are some similarities between the airway inflammation seen in patients with severe asthma, smokers with asthma, and those with COPD, which might indicate that there are several common mechanisms of steroid resistance between these diseases [78, 80].

There are no biomarkers that can be quantified for corticosteroid resistance. There are several molecular pathways that lead to corticosteroid resistance. Unravelling these pathways will allow the identification of novel targets for therapy.

Possible cellular mechanisms associated with corticosteroid resistance include [81–83]:

1) Dysfunction or genetic abnormalities of the cytoplasmic receptor of corticosteroid glucocorticoid receptor-α (GR-α): a) due to increased phosphorylation of kinases (p38 mitogen-activated protein kinase α and/or γ, c-Jun-N-terminal kinase I), leading to decreased nuclear translocation; b) due to increased IL-2, IL-4 and IL-13, leading to decreased phosphorylation of GR-α, and subsequently to decreased nuclear translocation; and c) due to an increase of inducible nitric oxide synthase.
2) Increased GR-β in epithelial cells, due to increased IL-17.
3) Histone acetylation, due to decreased histone deacetylase 2, leading to decreased inflammatory gene repression.
4) Increased expression of proinflammatory transcription factors: activator protein-1 (AP-1) and NF-κB.

Novel mechanisms behind corticosteroid resistance observed primarily in animal studies include: altered expression of microRNA 9 and 21; increased signalling of phosphatidylinositol-3-kinase (PI3K), Toll-like receptors (TLR); increased expression of nod-like receptor protein-3 inflammasomes/IL-1β, TNF-α, interferon γ (IFN-γ), TNF-related apoptosis-inducing ligand, TSLP; reactive oxygen species (ROS); pathogens such as *Chlamydia* and viruses, such as HRV-IB, RSV, and *Aspergillus*; exposure to allergens such as house dust mite and ovalbumin; transforming growth factor-β (TGF-β) disrupting the balance between GR-α in favour of GR-β; and IL-33. Finally, obesity/high fat diet and air pollution have also been implicated [82, 84].

Table 1 outlines the management of corticosteroid resistance in asthma [85]. The addition of biologics, such as mepolizumab [86], benralizumab [87] or dupilumab [88], in patients who had severe asthma has contributed significantly in reducing the dose or withdrawing oral corticosteroids (figure 1).

The therapeutic strategies for corticosteroid insensitivity in asthma and COPD are shown in table 2.

There are several emerging therapies targeting T-helper (Th)17 cell responses in corticosteroid-insensitive asthma. They include (with the target molecule given in brackets): anti-IL-17A and secukinumab/CJM112 (IL-17A), brodalumab (IL-17RA), atlizumab and tocilizumab (IL-6R), canakinumab (IL-1β), anakirna (IL-1R1) and ursolic acid (RORγt), among others [80].

Therapeutic candidates for reversing corticosteroid resistance in experimental models include clarithromycin, trametinib and tofacitinib pimozide for severe asthma; artesunate for COPD/asthma; and aclidinium bromide, rapamycin, roflumilast N-oxide, carbocysteine, quercetin, curcumin and others for COPD [83].

TABLE 1 Management of corticosteroid resistance in asthma

1	Diagnosis of asthma through history, physical activity and laboratory investigation. Exclude disorders that may give similar symptoms, *e.g.* sinusitis, gastro-oesophageal reflux, tracheomalacia and vocal cord dysfunction.
2	Identify and remove the patient from environments with potential allergens that may cause asthma.
3	Administration and compliance with appropriate medications.
4	Exclude psychological factors that may affect asthma and/or adherence to prescribed regimens.
5	Assess patients for potential concomitant microbial infection of the airways.
6	Control the symptoms by appropriate combination therapy.
7	Evaluate the pharmacokinetics of systemic corticosteroids to maximise pulmonary function. As an alternative therapy consider *i.m.* administration of triamcinolone. In cases of rapid elimination of corticosteroids, the daily dosing regimen may be split, with the second dose administered in the afternoon.
8	If despite treatment with corticosteroids there is persistent tissue inflammation, assess sputum eosinophils, bronchoalveolar lavage, exhaled nitric oxide or biopsy specimens.
9	Consider alternative anti-inflammatory and immunomodulatory therapies.

Information from [85].

In conclusion, a major barrier to effective management of asthma is the possibility of reduced responsiveness to the anti-inflammatory effects of corticosteroids. This is more often observed in smokers, patients with severe asthma and in the majority of patients with COPD. Several molecular mechanisms may account for reduced corticosteroid responsiveness in patients with severe asthma, such as reduced nuclear translocation of the corticosteroid-GR-α cluster. Other possible mechanisms include increased secretion of macrophage migration inhibitor factor; increased expression of GR-β, which competes with and thus inhibits activated GR-α; and competition with the transcription factor AP-1. In severe asthma, smokers with asthma and COPD, the expression and activity of histone deacetylase 2 are reduced by oxidative stress due to activation of phosphoinositide 3-kinase δ. New targets for therapy have been identified as we unravel the molecular mechanisms leading to corticosteroid resistance.

Comorbidities and drug interactions (Mario Cazzola)

According to current evidence from extensive studies and quantitative synthesis of published reports, asthma and COPD are frequently associated with various comorbidities, including cardiovascular (CV) disease (CVD), depressive disorders, type 2 diabetes mellitus (T2DM), osteoporosis, malignant pulmonary neoplasms, skeletal muscle wasting, and cachexia. Many of these comorbidities have been linked to systemic inflammation and may impact asthma and COPD severity and intensity [90–92]. While data show

Study	Biologic	Oral corticosteroid dose				
		% reduction			≥90% reduction	
		Placebo	Drug	p-value	Placebo	Drug
SIRIUS [86]	Mepolizumab (100 mg)	0%	50%	0.007	11%	23%
ZONDA [87]	Benralizumab (30 mg)	25%	75%	<0.001	12%	Every 4 weeks dose: 33% Every 8 weeks dose: 37%
VENTURE [88]	Dupilumab (300 mg)	41.9%	70.1%	<0.001	30.8%	55.3%

Mepolizumab	Benralizumab	Dupilumab
Yes reduce + withdraw	Yes reduce + withdraw	Yes reduce + withdraw

FIGURE 1 Biologics: mepolizumab [86], benralizumab [87] or dupilumab [88] significantly reduce the dose of or withdraw oral corticosteroids in patients with severe asthma.

TABLE 2 Therapeutic strategies for corticosteroid insensitivity in asthma and COPD

Therapeutic strategy	Mechanism of action		Drugs
Alternative broad-spectrum anti-inflammatory drugs	Inhibitors of calcineurin		Ciclosporin, tacrolimus
	Immunomodulators		Methotrexate
	Inhibitors of phosphodiesterase (PDE)4		Roflumilast, cilomilast
	Inhibitors of p38 mitogen-activated protein (MAP) kinase		
	Inhibitors of inhibitor kappa-B kinase β (IKKβ)		
Reversing steroid resistance	Inhibitors of p38 MAP kinase		
	Inhibitors of c-Jun N-terminal kinase (JNK)	Decrease activator protein-1 (AP1)	
	Vitamin D in steroid-resistant asthma	Increases regulatory T-cells	
	Inhibitors of macrophage migration inhibitor factor (MIF)		
	Inhibitors of P-glycoprotein		
	Activators of histone deacetylase 2		Theophylline
		Inhibitors of phosphoinositide 3 kinase δ	Copanlisib, idelalisib, umbralisib
		Antioxidants	
		Inhibitors of inducible nitric oxide synthase (iNOS)	
Increase corticosteroids responsiveness	Long-acting β_2-agonists	Reverse glucocorticoid receptor-α (GR-α) phosphorylation	

Information from [89].

that systemic inflammation is the common connection between asthma, COPD, and numerous comorbidities, particularly CVD and T2DM, the systemic component's mechanisms remain unknown.

The treatment of asthma and COPD is essentially based on bronchodilators, possibly associated with each other and/or ICSs. According to current thinking, even in the presence of CVD or T2DM, these two lung disorders should be treated as usual.

Nonetheless, reports of adverse CV events in patients with asthma or COPD who are on LABA or LAMA should prompt clinicians to evaluate this risk. In effect, the presence of β_1 and β_2 AR and M_2 and M_3 MR in the heart suggests that both LABA and LAMA impact the heart, even when they are very selective. This impact may be especially relevant for individuals with underlying cardiac disorders, albeit those with heart failure frequently have bronchoconstriction that is reversible with inhaled β_2-agonists. The resulting decrease in breathing effort might reduce cardiac workload even more [93–98]. Furthermore, there is evidence that in patients with pulmonary hyperinflation, which is frequent in both asthma and COPD, dual bronchodilation improves regional ventilation and blood flow in the pulmonary microcirculation. This may, in turn, contribute to improvements in cardiac filling and cardiac output [97].

Unfortunately, only a few studies have investigated the impact of bronchodilators on non-CV comorbidities, and in asthma patients, they have been even fewer. For example, it has been suggested that β-agonists can affect glucose homeostasis through modulation of insulin secretion, production of hepatic glucose, secretion of glucagon, and glucose uptake into the muscle. However, these effects are of little clinical significance, except in patients with borderline glucose intolerance. The sensitivity of β-agonists may be affected by hypoglycaemia. Conversely, β-agonists may play a role in treating or preventing hypoglycaemia. In any case, β_2-agonists exhibit protective effects against the vascular complications of diabetes that seem to be dependent on a β-arrestin2/inhibitor of kappa B (IκB)/NF-κB signalling pathway. β_2-AR activation increases the levels of β-arrestin2 and its interaction with IκB, resulting in reducing inflammatory stimulus and offering tissue protection [99, 100].

It is obvious that while waiting for additional research, the existence of comorbidities should influence bronchodilator selection, focusing on minimising the risk of possible side-effects and medication interactions.

There is no indication that ICS medication for asthma or COPD increases the incidence of CV events. While observational studies imply that these drugs have favourable effects on the CV system, data from

major clinical trials, notably those conducted in individuals at high CV risk, are less definitive. Emerging results show that ICSs positively affect CV risk and mortality when used in a triple treatment. Nonetheless, while these findings are intriguing, they require additional investigation.

Corticosteroid use has been linked to an increase in the prevalence of T2DM in those with asthma or COPD, although some recent studies have not indicated an increased risk of diabetes among ICS users. It has been suggested that addressing pro-inflammatory cytokines that are overexpressed in individuals with asthma and CVDs may improve clinical results dramatically [101].

β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 (AT1) receptor blockers, statins, antiplatelet drugs, calcium-channel blockers, and diuretics are commonly used to treat the various CVDs, independent of whether the patient also has asthma or COPD.

Many clinicians withhold β-blockers from patients with chronic airway diseases due to concerns about bronchoconstriction and the neutralisation of β_2-agonist efficacy. Several studies show that nonselective β-blockers should not be used to treat CVD in asthma patients. In persons with asthma and CVD, the deleterious respiratory response to β-blockers varies depending on β_1-AR selectivity, dosage, and length of exposure. If cardioselective β_1-blockers are required for acute CVD, and no other treatment choices are available, asthma is not an absolute contraindication; nonetheless, current cardioselective β-blockers still pose a danger to asthma patients. Observational trials and retrospective analyses, on the other hand, suggest potential advantages of β-blockers in COPD with or without CVD. β-blockers may have therapeutic benefits in people with COPD independent of CV effects because of the decreased sympathetic tone and activation of β_2-ARs in the lung. There is intriguing experimental evidence of a synergistic interaction between the U-LABA agonist indacaterol and the selective β_1-AR antagonist metoprolol in lowering infarct size and normalising and reversing cardiac remodelling. Furthermore, even when a β-blocker is included, there is no danger in treating individuals with CVD and simultaneous COPD with dual bronchodilation [97].

The renin–angiotensin system may have a role in the pathophysiology of asthma and COPD by generating proinflammatory mediators in the lungs. As a result, ACE inhibitors and AT1 receptor blockers may benefit people with asthma or COPD.

Statins also have several pharmacological properties that may be useful in treating individuals with asthma or COPD, such as antioxidant, anti-inflammatory, and immunomodulatory effects.

Antiplatelet drugs may benefit patients with bronchial asthma and COPD, since platelets are more activated in these patients than in healthy controls. An additional benefit of antiplatelet therapy is that in these inflammatory disorders, the functions of platelets are distinct from those during haemostasis and clot formation. Thus, antiplatelet drugs may also modulate lung inflammatory responses.

Calcium channel blockers help enhance lung function, particularly in exercise-induced asthma. Long-term nifedipine treatment might prevent a decline in cardiac output in COPD patients with high pulmonary pressure. However, dihydropyridine calcium channel blockers have the potential to be detrimental due to poor ventilation/perfusion matching and increased hypoxaemia.

Concurrent use of β_2-agonists, theophylline or ICSs with a diuretic, primarily a thiazide, may amplify hypokalaemia effects, leading to arrhythmia. Therefore, patients with COPD or asthma who are on potassium-wasting diuretics and have persistent respiratory acidosis or are taking ICSs or β_2-agonists should have their electrolyte levels regularly evaluated and be considered for potassium supplementation, and preferably potassium-sparing drugs.

It would be logical to explore treating systemic inflammation as a viable way to concurrently treat asthma or COPD and T2DM when they coexist. In patients with diabetes, the impairment in lung function can lower the threshold for clinical manifestations of asthma or COPD. Therefore, it is imperative to control high glucose levels that can lead to the enhanced responsiveness of human ASM. In T2DM patients, neither metformin nor insulin improved lung function, but glucagon-like peptide-1 receptor (GLP-1R) agonists improved it. Therefore, GLP-1R might be a novel therapeutic target for treating T2DM when coexisting with asthma or COPD [102, 103].

Managing patients with asthma or COPD with comorbidities necessitates regular supervision of medication usage and a thorough evaluation of the prescription list at each presentation. Every effort must be made to

decrease the risk of adverse effects on the airways and organs affected by comorbidity. Given the current emphasis on treating patients with chronic airway problems based on treatable traits, we must not forget that comorbidities are essential extrapulmonary treatable traits that require specialised therapy when present [104].

Precision medicine in asthma: pharmacogenomics and beyond (Anke-Hilse Maitland-van der Zee)

Asthma comprises multiple phenotypes, which might be treated with different types of innovative-targeted therapies. Understanding the underlying biological structure of these phenotypes would help to apply precision medicine approaches. Recent technological advancement in omics methods (table 3) has enhanced the investigation of asthma from diverse angles. The use of these technologies has reduced the gap from bench to bedside; nevertheless, several methodological challenges remain to be tackled before omics can be applied in the care of patients with asthma. Collaborating under a centralised, harmonised framework (such as in consortia, under consistent methodologies) could help worldwide research teams to tackle these challenges [105]. Examples of the use of different omics layers in precision medicine in asthma include the pharmacogenomics of ICS [106, 107] and of LABA [108]. Genotyping the Arg16Gly polymorphism in the β_2-AR might be a good way to identify children that will not have a therapeutic response to LABA.

A multi-omics approach can be used to study phenotyping of non-eosinophilic asthma. Starting with the sputum microbiome and adding several other layers of omics enabled the distinction of a specific phenotype of non-eosinophilic asthma and some treatment options for this phenotype [109, 110]. This can help the identification of the cluster 2 microbiome-driven asthma phenotype: a subtype within corticosteroid-resistant asthma patients. It can offer therapeutic options: antibiotics (*e.g.* macrolides) or phage therapy, and in addition, new other therapeutic targets for cluster 2 patients. Neutrophilic asthma is not a single phenotype and underlying mechanisms should be considered to optimise treatment.

Measurement of volatile organic compounds (VOCs) in exhaled breath ("breathomics") *via* an electronic nose and gas chromatography–mass spectrometry analysis of VOCs, enabled the distinction of different phenotypes of asthma [111]. This can also help to identify a viral or bacterial infection before the patient experiences symptoms. In the future this might be helpful to prevent exacerbations [112–114].

Challenges for clinical development: European Medicines Agency (EMA) regulations for asthma and COPD drug approval

Key challenges faced for approval of anti-inflammatory drugs for asthma and COPD: EMA perspective (Laura Fregonese)

Disclaimer: the views presented in this text are those of the author and should not be understood or quoted as being made on behalf of the EMA and/or its scientific committees. They do not replace any guidance given in published EMA guidelines, and do not intend to replace and prejudice any scientific assessment the EMA/Committee for Medicinal Products for Human Use (CHMP) makes on product-specific applications.

TABLE 3 Use of omics for the investigation of asthma

Breathomics	Is a branch of metabolomics that quantifies volatile organic compounds collected from human exhaled samples or exhaled breath condensate samples using gas chromatography–mass spectrometry and gas sensor-driven electronic nose (eNose).
Epigenomics	The study of all of the epigenetic modifications in a cell. Epigenetic changes are changes in the way genes are switched on and off without changing the actual DNA sequence.
Exposomics	The application of internal, general external and specific external exposure assessment methods to study the exposome, which can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health.
Genomics	The study of the structure, function, evolution, mapping, and editing of genomes.
Metabolomics	The study of chemical processes involving metabolites, intermediates and products of cell metabolism.
Microbiomics	The science of collectively characterising and quantifying molecules responsible for the structure, function, and dynamics of a microbial community.
Pharmacogenomics	The study of the role of the genome in drug response.
Proteomics	The study of the structure and function of proteins, including the way they work and interact with each other inside cells.
Transcriptomics	The examination of whole transcriptome changes and their functions across a variety of biological conditions. The transcriptome is the sum of all of its RNA transcripts.

Information from [105].

The EMA is the medicines' regulatory body of the European Union (EU). The main remit of EMA is that of authorising new medicines through CHMP. However, the role of EMA extends far beyond the authorisation of medicines and follows new medicines along their whole lifecycle, including provision of scientific advice on clinical development as well as on quality and non-clinical issues, agreement on paediatric clinical studies by paediatric investigation plans (PIPs), and post-marketing activities, *e.g.* monitoring long-term safety of medicines and their use in special populations, among others.

The medical devices regulation (regulation (EU) 2017/746), which came into force in the member states of the EU in May 2021, gave EMA additional responsibilities in the area of medical devices. The regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns. In the frame of the regulation, the EMA has remit on medicines with an integral device, such as pre-filled inhalers, and is involved in a wide range of other devices.

The regulation also includes companion diagnostics, defined as devices that are "essential for the safe and effective use of a corresponding medicinal product to:

1) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
2) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product".

Anti-inflammatory medicinal products have been the cornerstone of the treatment of asthma and COPD for decades. While innovation in terms of mechanisms of action of anti-inflammatory treatments for asthma and COPD have been limited, knowledge of the pathophysiology and clinical manifestations of these diseases have evolved, highlighting individual differences and the importance of phenotypes and endotypes that may benefit from personalised treatment. This, together with emerging knowledge of different responses (beneficial and noxious) to the available treatments in populations affected by asthma and COPD, is leading to the search for specific treatable traits.

One of the traditional challenges in authorising anti-inflammatory medicines for asthma and COPD is the quest for endpoints that are easy to measure and clinically relevant. For asthma, the EMA guidelines (last updated in 2016) recommend exacerbations as a primary endpoint of clinical efficacy for anti-inflammatory treatments. However, measuring exacerbations may require large sample sizes and long observation periods, may be suboptimal in early/milder disease stages, and enriching study populations based on frequency of exacerbations may lead to limitations in generalisability. Differences in the definition of exacerbations across clinical studies may further complicate interpretation of data and comparability of results. Lung function endpoints (FEV_1) as a surrogate of clinical efficacy are not considered sufficient by the EMA guidelines as single primary endpoints in pivotal clinical trials for licensing. The most recent fixed-dose combination products for the treatment of asthma were authorised based on co-primary endpoints usually containing exacerbations, or primary and key secondary endpoints of exacerbations and lung function. Similar reasoning applies to COPD, with the additional limitations of using lung function as surrogate in, for example, COPD phenotypes where emphysema is prevalent. Alternative outcome measures such as those reflecting lung structure changes in COPD (*e.g.* CT scan densitometry) have been discussed in the frame of specific regulatory applications, but are not widely accepted as primary endpoints.

In the clinical development of asthma and COPD products, patient-reported outcomes (PROs) are mainly used as secondary endpoints in phase III clinical trials, and in some cases as co-primary endpoints. While increasing the use of PROS would help capturing different aspects of the disease, one hurdle to their use for regulatory purposes is validation. The EMA offers a methodologies' qualification programme for endpoints, biomarkers, designs, and patients' selection tools, among others. PROACTIVE in COPD (including PROs and activity monitoring) and EXACT-PRO (EXAcerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome) were validated *via* such procedures. While the qualification procedure can be time and resource consuming, it does allow agreeing with regulators on scopes and breadth of use within EMA procedures. The use of specific PROs as part of composite endpoints for regulatory approval can also be discussed in relation to specific developments during scientific advice procedures at EMA and agreed, for example, in the context of a given study protocol.

Because asthma and COPD treatments are often product/device combinations, regulators are used to handling scientific and regulatory aspects of inhalation devices in asthma and COPD and take into account devices' specifications and performances in the assessment of quality and of the overall benefit/risk assessment. For example, guidelines exist for fixed-dose combination products including those by inhalation, as well as for orally inhaled products in asthma and COPD. The new regulation on medical

devices enlarges the remit of regulatory agencies and notified bodies on companion diagnostics, as mentioned above, which may facilitate the road to a more integrated approach to medicines' development along with specific diagnostic tools, by putting them under the same regulatory umbrella.

The use of digital health technology (DHT), connected to devices, or as monitoring tools of endpoints and treatment adherence, and for many other purposes is becoming more and more frequent and adds a layer of complexity that the EMA is addressing with several specific initiatives and *ad hoc* expert groups. Digital technologies need to be considered adequate/qualified when they are relevant to the product in a way to have an impact on its benefit/risk. The use of digital technologies, as well as of other devices, includes the need for human factor studies in addition to clinical studies, in order to assess the usability of the DHT tool. The first asthma inhaler with a medical device consisting of a sensor plus a digital app, and used with smartphone technology, which senses, records actuations and doses taken and transfers the information *via* Bluetooth to a smartphone app was authorised at the EMA in 2020.

Increasing collaboration between researchers, clinicians, patients and regulators will be beneficial to identify endpoints and methodologies, including digital tools, that are suitable for capturing different dimensions of asthma and COPD and may aid clinical trial conduction and treatment adherence, thereby facilitating the authorisation of new medicines for asthma and COPD.

What is this seminar's position on the selection of treatment in asthma and COPD?

Identifying surrogate markers and outcomes

Which surrogate markers can be used to assess and quantify disease in a preclinical stage? Do we need drug intervention in preclinical detectable disease? Chair: Dave Singh

The focus of the discussion was the possible value of a potential study in subjects with "preclinical" COPD.

Different definitions were discussed: "early COPD", "young COPD", "PRE-COPD", "PRISM" (definitions according to Global Initiative for Chronic Obstructive Lung Disease 2022). A target population was agreed as follows: subjects without spirometrically confirmed airflow obstruction (*e.g.* $FEV_1/FVC > 0.7$) but who have 1) a history of exposure to noxious particles, and 2) respiratory symptoms. It was felt that the above population was at high risk of developing COPD but did not yet fit the formal definition for inclusion into studies.

Age was discussed. It was agreed that older individuals with the above features may never develop COPD, but the age cut-off to apply was unclear. While one could study younger subjects (*e.g.* <60 years), it was felt that having a cut-off of 65 or 70 years of age was more inclusive of an ageing population.

Measurements of interest would be: high-resolution CT – lung density, pi10; diffusing capacity of the lung for carbon monoxide; oscillometry; multiple breath washout; spirometry; and evaluating sputum symptoms/airway infection.

Outcomes: observational or interventional studies may be undertaken in such a population. An observational study would elucidate risk factors for developing COPD. An interventional study would identify how to stop the development of COPD. Disease progression would be the outcome, as evaluated by lung function or CT scan.

Which are the read-outs to assess drug effect in the progression of the disease? Chair: Paola Rogliani

Obstructive diseases must be redefined. It remains to be clarified if a treatable trait is the answer to measure or assess drug effects. It is necessary to find measurements for assessing a drug beyond FEV_1 and exacerbation. Hyperinflation and PROs should be studied. It could be useful to use composite endpoints, such as clinically important deterioration, but use them in perspective assessment. It will be helpful to focus on the treatment of exacerbation along with an appropriate definition in terms of biology, molecular, intensity, duration and severity. Molecular characterisation/determination in a preclinical model, such as organoids, may be useful for the study of exacerbations.

Is an effect on remodelling required for drug efficacy? If so, how to assess it? Chair: Alexander G. Mathioudakis

Remodelling represents a critical process that needs to be rigorously evaluated, as it could reveal targets for new treatments that could potentially prevent or reverse the long-term damage caused by airway diseases. Remodelling as an outcome could be a surrogate for disease progression. However, it is not yet validated. There are other measures that have been better validated for assessing disease progression (*e.g.* airflow

limitation or the extent of emphysema in CT scans). These latter instruments could perhaps be used as surrogate measures for remodelling.

Is remodelling a patient-relevant outcome? It was suggested that to patients it is more relevant to know whether a novel treatment will limit their symptoms, prevent exacerbations, or prolong their lives (hard outcomes). However, in asthma/COPD outpatient clinics, patients are interested to hear whether their disease will progress or whether there are any treatments that could reverse the changes that their diseases have caused to their lungs. Therefore, it is important to assess this outcome. However, treatments that improve the symptoms and exercise capacity and/or prevent exacerbations, without reversing the remodelling, can also be valuable for patients with chronic airway diseases. Therefore, it is important to look for drugs that will have an effect on remodelling, but the group did not feel that an effect on remodelling is required for drug efficacy.

Accurate quantification of remodelling is another important issue. Remodelling is a very complex process, involving several pathways and, to our knowledge, there is no validated measure of assessing the overall impact of interventions on remodelling. We can assess the impact on extracellular matrix, or on the airway wall thickness, or on alveoli, *etc*., but we do not have an overall/overarching tool. Therefore, there is an urgent need to develop effective instruments for assessing remodelling. Invasive samples from bronchoscopies may be needed at present. Ideally, we need to develop noninvasive markers that could be used more broadly in research, as well as clinical practice.

How do we select treatments for patients with severe asthma and COPD?

What is the non-clinical evidence to sustain combination therapy including ICS in COPD? Chair: Dave Singh

Mario Cazzola discussed the various studies he has undertaken showing additive and synergistic effects of ICS, LAMA and LABA on ASM.

The past few years have brought a wealth of data that higher blood eosinophil counts are related to greater ICS benefits in COPD patients with a history of exacerbations. This is related to greater T2 inflammation (with higher eosinophil counts). Airway neutrophilic inflammation is relatively resistant to steroids [115] and human lipopolysaccharide challenge models [116]. ICS, therefore, target a T2 component of COPD inflammation.

Which features suggest considering patients for non-pharmacological interventions in asthma and COPD? Chair: Alexander G. Mathioudakis

Three groups of interventions are discussed.

1) Simple, affordable and broadly used interventions such as vaccinations (influenza/pneumonia/coronavirus disease 2019 (COVID-19)), smoking cessation, noninvasive ventilation, or pulmonary rehabilitation. The safety and effectiveness of such interventions have been extensively validated and have clear indications supported by national and international guidelines. The only problem is the adequate and timely administration of these interventions. For example, in many countries, even in Europe, pulmonary rehabilitation is only offered through secondary care, and after patients have had several admissions for COPD exacerbations. However, earlier pulmonary rehabilitation could allow these patients to change their lifestyle earlier and gain larger benefits. Also, earlier in the natural history of the disease, patients may have better reserve and could more easily/extensively change their lifestyle. Similarly, the importance of repeating pulmonary rehabilitation after each hospitalised exacerbation has been established, but this aim is not yet achieved in most countries, as adequate resources/slots for pulmonary rehabilitation are lacking. Primary care should be incentivised to look for indications for non-pharmacological interventions and to offer them early. There are concerns that due to the resources and coordination required for delivering these interventions, equity is lacking across Europe, since several countries are not able to adequately deliver them.
2) More complex and expensive interventions, such as lung volume reduction or thermoplasty, should initially take into consideration their high cost and the associated risks. For example, pneumothorax with persistent air leak after bronchoscope lung volume reduction. Patients should be carefully selected, focusing on cases where these interventions could make a significant difference (acceptable risk/benefit outcome). Criteria are well defined, with globally agreed indications, but need continuous re-evaluation, as new therapeutic options emerge. For example, the emergence of biological treatments for asthma (benralizumab/mepolizumab/reslizumab/dupilumab/tezepelumab) has significantly limited the indication for thermoplasty.
3) Shielding and isolation, a measure that was applied for COVID-19, had positive effects in the exacerbation rates of patients with airway diseases. However, the adverse effects of such interventions

(social isolation, depression, deconditioning, *etc*.) that have been established by far outweigh any potential benefits and they should not be recommended for COPD or asthma.

How to streamline clinical and basic research

How can academia and industry cooperate in translating relevant clinical questions to experiments? Chair: Jørgen Vestbo

The area of pharmacology of asthma and COPD seems a natural area of collaboration between academic respiratory medicine and the pharmaceutical industry. There are three areas of importance.

1) Any collaboration between academia and industry comes with inherent challenges and needs to be considered carefully, requires complete transparency, and often requires a number of approvals from the academic institution/hospital, and involves contracts between the academic researcher and industry. Most important, however, is trust, and in this respect collaboration between academia and industry does not differ from collaborations within academia.
2) For the academic, collaboration with industry will often feel very different as it is usually more of a "business agreement" rather than an informal collaboration, and the financial aspects require careful considerations from both parties. Here, the relationship is comparable to the traditional Jewish wedding dance – dancing without touching.
3) Considering what major value the academic provides, disease understanding must be top of the list, and there is a general agreement that lack of new compounds are due to lack of provision of disease mechanisms and pathways to be targeted for industry. Often, a respiratory academic will provide valuable insight into study design, conduct and outcomes, and a successful collaboration will likely result in more applicable study findings. There were several examples of good and long-lasting collaborations, but also a realisation that the most immediate future collaborations will be with smaller biotech companies.

There is a general discussion to be had around clinical trials. Currently, the costs and efforts of doing investigator-initiated and -led trials are so extensive that for practical purposes they are inhibitory for doing the trials. Apart from costs, the ever-increasing governance requirements, a growing bureaucracy, and time-requiring meetings with ethics committees, contract officers, hospital R&D, *etc.* is likely to make any interested young would-be-trialist leave for other areas of medicine. This is a very real threat to progress in management in general, including asthma and COPD.

There is also a general question as to the appropriateness of industry deciding which trials are needed and carried out, and increased means for doing more investigator-led trials are urgently needed. A suggestion at the symposium was to lobby internationally for an increase of tobacco industry revenues to be used for research in respiratory disease, an area the European Respiratory Society (ERS) could lead.

How to translate experimental data to clinical practice? Chair: Reinoud Gosens

One of the most important discussion points that came up is that successful translation requires multiple parties and stakeholders and accordingly, it is of vital importance to have all parties on board early on. This includes basic scientists and clinicians as well as patients and experts on development of investigational products for early preclinical findings to ensure the right steps are taken in a timely and effective order. To ensure translation of basic science into clinical applications it is equally important to work with cell and *in vivo* models that have translational value and to include human *in vitro* disease models where possible and relevant. *Vice versa*, there is a need for molecular and cellular biomarkers derived from patient studies that help to predict clinical progression, and which may be used as approximates in preclinical studies to facilitate translational success. From the perspective of developing an investigational product, it will be key to reduce risks for translational success and to have equal focus on risk reduction and preclinical efficacy, as both are required for translational success. To combat problems with translation associated with reproducibility, it will be essential to publish negative results and to accurately and completely report methods.

Which themes should be prioritised? Chair: Maia Rukhadze

- The current gaps between asthma and COPD care should be closed and there should be equal access to the treatment for asthma and COPD globally.
- Enhance the collaboration of health communities from countries and ethnic groups of different socioeconomic status.
- Increase the awareness about asthma, COPD and other chronic respiratory conditions.
- Enhance the collaboration between health professionals, policy makers and patient organisations to identify early prevention measures, diagnostic determinants, relevant biomarkers, precise

measurements, and discover new horizons and strategies for innovative treatment for asthma and COPD.
- Invite regulatory bodies onto ERS boards, obtain access to important international foundations, and increase the voice of our clinical community worldwide.
- Gain governmental support to eliminate the negative impact of tobacco smoke through a large-scale campaign to stop smoking; increase taxes on tobacco at the local and global level.

Funding issues for medical research

The members of the seminar agreed on the following issues:
- Basic but particularly clinical research is becoming more complex, expensive and time consuming.
- Medical personnel are hesitant about participating in medical research, as they have to work on weekends to generate data.
- Although the EU, healthcare authorities and other organisations support research, funding of medical research depends heavily on pharmaceutical industry.
- Support and funding for investigator-initiated research, which is essential to answer specific clinical questions, declines continuously.
- Ethical issues in supporting medical research from money from self-insured patients treated in hospitals.
- ERS, the American Thoracic Society and other influential international societies should lobby at the highest possible level in Europe, the USA and worldwide to enforce legislation that a percentage of the taxation from different sources should be directed into a special fund, run by an international independent committee, to fund basic and clinical, investigator-initiated research from: tobacco industry; carbon dioxide tax (*e.g.* European Green Deal), from sectors that generate a high level of emissions, such as electricity, concrete and steel industries; and chemical, pesticide, fertiliser industries, *etc*. The rationale is that such industries, through tobacco smoking and pollution of the environment, increase the number of people that will suffer, among others, from lung diseases (asthma, COPD), cancer, *etc.*, which will eventually increase the burden on national health systems. The pharmaceutical industry should also be included, as it has made enormous profits due to the continuing COVID-19 pandemic.
- Other issues raised included the added obstacles in research that are attributed to the running of ethics committees, research committees, and indirect costs (*e.g.*expenses for the general operation of an organisation, officers' salaries, accounting department costs and personnel department costs). Of course, these parameters differ between countries and between different hospitals and research institutions, but very often they hinder research efforts.

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