# Barriers to new drug development in respiratory disease

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**The 2014 ERS Presidential Summit discusses how development of new respiratory drugs can be accelerated** http://ow.ly/IcOsZ

## Introduction

Despite enormous unmet medical needs in respiratory medicine, very few new classes of safe and effective therapy have been introduced over the past 40 years. In spite of its enormous burden, respiratory medicine appears to have fewer new approved therapies than other common disease areas, such as cardiovascular, metabolic and neurological diseases, with fewer drug candidates and a higher failure rate. Furthermore, as in other areas of drug discovery, the time for drug development is getting longer and the risk of failure ever higher, leading to enormous and growing development costs. In order to identify some of the barriers to drug discovery in respiratory medicine, a European Respiratory Society Presidential Summit was held on July 2–3, 2014, in Rome, Italy. This meeting brought together respiratory scientists, clinicians, regulators, clinical pharmacologists and the pharmaceutical industry from across Europe to explore how these barriers might be overcome to facilitate the future development of new and effective therapies for respiratory diseases. This editorial highlights some of the opportunities for improving respiratory drug development that were discussed at the 2014 European Respiratory Society Presidential Summit. These include the development of more predictive preclinical disease models, the regulatory framework needed for better respiratory drug development, and how Germany is hoping to address the issues discussed above through a recently established national centre for lung research.

## Unmet needs in respiratory medicine

Respiratory diseases represent an enormous and increasing healthcare and economic burden across Europe, with over 600 000 deaths a year and six million hospital admissions with total costs exceeding €380 billion per year [1]. Globally, respiratory diseases are amongst the leading causes of death, with chronic obstructive pulmonary disease (COPD) now the third and fourth ranked cause of death in Western Europe and worldwide, respectively [2]. Lung cancer has an unacceptably high mortality rate and is the most common cause of death amongst all cancers, accounting for 20% of all cancer deaths in Europe. Indeed, COPD and lung cancer alone account for >50% of deaths from respiratory disease in Europe, yet there has been little impact of drug therapy on this high mortality for either disease. Asthma is now one of the most prevalent diseases in Europe and affects people of all ages but, despite effective therapies, many patients are poorly controlled and have a low quality of life [3]. More effective treatments

Received: Jan 17 2015 | Accepted: Jan 19 2015

Conflict of interest: B. Ward is an employee of the European Respiratory Society. Further disclosures can be found alongside the online version of this article at erj.ersjournals.com

TABLE 1 Top selling respiratory drugs in 2012

| Rank | Drug | Brand | Company | Drug class | Sales $ bn |
|---|---|---|---|---|---|
| **1** | Fluticasone propionate/salmeterol | Seretide/Advair | GlaxoSmithKline | ICS/LABA | 8.0 |
| **2** | Tiotropium bromide | Spiriva | Boehringer Ingelheim | LAMA | 4.6 |
| **3** | Montelukast | Singulair | Merck | LTRA | 3.9 |
| **4** | Budesonide/formoterol | Symbicort | AstraZeneca | ICS/LABA | 2.8 |
| **5** | Fluticasone propionate | Flixotide/Flovent | GlaxoSmithKline | ICS | 1.2 |
| **6** | Salbutamol/ipratropium | Combivent | Boehringer Ingelheim | SABA/SAMA | 1.1 |
| **7** | Salbutamol | Ventolin | GlaxoSmithKline | SABA | 1.0 |
| **8** | Budesonide | Pulmicort | AstaZeneca | ICS | 0.87 |
| **9** | Omalizumab | Xolair | Roche | Anti-IgE | 0.75 |
| **10** | Methylprednisolone | Medron | Pfizer | Corticosteroid | 0.5 |

Data are based on reported company sales figures. ICS: inhaled corticosteroid; LABA: long-acting $\beta_2$-adrenergic agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonists; SABA: short-acting $\beta_2$-agonist; SAMA: short-acting muscarinic antagonist. Reproduced from [5].

are needed for patients with severe asthma who cannot be controlled with existing therapies. Multidrug-resistant tuberculosis (TB) poses a major threat in Europe with a lack of effective therapies and the risk of transmission amongst deprived populations. Only amongst rarer lung diseases, such as pulmonary hypertension, interstitial lung disease and cystic fibrosis, have there been any advances in drug therapy. More effective treatments are urgently needed in order to reduce the enormous suffering from lung disease and its high mortality.

## New therapies for lung disease

Most of the "new" treatments approved for respiratory diseases have been improvements on existing classes of drug, such as long-acting $\beta_2$-agonists, long-acting muscarinic antagonists, safer inhaled corticosteroids (ICS) and longer acting antibiotics. The world market for asthma and COPD drugs alone was $34bn in 2012 and is predicted to reach over $40 billion by 2017, with continued growth beyond 2023 as the global prevalence of these diseases increases and more patients are diagnosed [4]. This growth is almost entirely due to long-acting inhaled bronchodilators, ICS, combinations of the two, and the introduction of generic combination inhalers and anti-leukotrienes. The current top 10 selling drugs in the respiratory field are shown in table 1 and represent few classes of drugs and few pharmaceutical companies, with GlaxoSmithKline (GSK), AstraZeneca and Boehringer Ingelheim being the most predominant [5]. The prediction for the next few years shows little change, apart from the introduction of new long-acting bronchodilators (table 2). There have been very few new classes of drug therapy introduced for the treatment of respiratory disease over the past 40 years (table 3). It has proved difficult to find new classes of drug that are even as effective as existing therapies or have a comparable safety record. The best-selling new class of drugs are leukotriene receptor antagonists, but these drugs, although safe, are poorly effective in controlling asthma. Several epithelial growth factor receptor inhibitors are now approved for treatment of lung cancers, but they are effective only in a small minority of patients. The

TABLE 2 Predicted top selling drugs in 2018[#]

| Rank | Drug | Brand | Company | Drug class | Sales $ bn |
|---|---|---|---|---|---|
| **1** | Fluticasone propionate/salmeterol | Seretide/Advair | GlaxoSmithKline | ICS/LABA | 5.2 |
| **2** | Budesonide/formoterol | Symbicort | AstraZenca | ICS/LABA | 2.8 |
| **3** | Vilanterol/umeclidinium | Anoro | GlaxoSmithKline | LABA/LAMA | 2.1 |
| **4** | Fluticasone furoate/vilanterol | Breo/Relvar | GlaxoSmithKline | ICS/LABA | 2.1 |
| **5** | Salbutamol | Ventolin | GlaxoSmithKline | SABA | 1.1 |
| **6** | Fluticasone propionate | Flixotide/Flovent | GlaxoSmithKline | ICS | 1.1 |
| **7** | Indacaterol/glycopyrronium | Ultibro | Novartis | LABA/LAMA | 0.95 |
| **8** | Umeclidinium | | GlaxoSmithKline | LAMA | 0.76 |
| **9** | Montelukast | Singulair | Merck | LTRA | 0.70 |
| **10** | Omalizumab | Xolair | Roche | Anti-IgE | 0.69 |

ICS: inhaled corticosteroid; LABA: long-acting $\beta_2$-adrenergic agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting $\beta_2$-agonist; LTRA: leukotriene receptor antagonists. [#]: excluding Boehringer Ingelheim. Reproduced from [5].


DOI: 10.1183/09031936.00007915

TABLE 3 New classes of drug introduced for respiratory diseases

| Drug class | Examples | Disease indication | Comments |
|---|---|---|---|
| **LTRA** | Montelukast and zafirlukast | Asthma | Weakly effective |
| **Anti-IgE** | Omalizumab | Severe asthma | Effective in selected patients |
| **PDE4 inhibitors** | Roflumilast | COPD | Low therapeutic index |
| **EGFR inhibitors** | Gefitinib and erlotinib | Lung cancer | Selected patients EGFR+ |
| **CFTR potentiators** | Ivacaftor | Cystic fibrosis | Only for G551D mutation (~4% of patients) |
| **Endothelin receptor-antagonists** | Bosentan, ambrisentan and macitentan | Group 1 pulmonary hypertension | Rare disease |
| **Soluble guanylate cyclase activators** | Riociguat | Group 1 and 4 pulmonary hypertension | Rare disease |
| **PDE5 inhibitors** | Sildenafil and tadalafil | Group 1 pulmonary hypertension | Rare disease |
| **Anti-fibrotic agents** | Pirfenidone and nintedanib | IPF | Rare disease |
| **Anti-tuberculous drugs** | Bedaquiline | Drug-resistant TB | Poor safety |

LTRA: leukotriene receptor antagonist; PDE: phosphodiesterase; EGFR: epidermal growth factor receptor; CFTR: cystic fibrosis transmembrane conductance regulator; COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; TB: tuberculosis.

other new drug classes have addressed rare diseases, where there is clearly an unmet need, but these drugs are necessarily very expensive and account for small global sales. Several new classes of drug have been introduced for the treatment of Group 1 pulmonary hypertension, including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase activators and prostanoids. Recently, drugs have also been approved for cystic fibrosis, but the cystic fibrosis transmembrane conductance regulator potentiator, ivacaftor, is only indicated for the rare G551D mutation, which is found in only 4% of patients with the result that the cost of this drug is around $300 000 per year. New anti-fibrotic drugs (*e.g.* pirfenidone and nintedanib) have also recently been approved for idiopathic pulmonary fibrosis, but the effect of these treatments is small, the side-effects troublesome and the disease rare, with limited survival. It has proved difficult to develop new effective antibiotics, but recently a new drug (bedaquiline) has been approved for the treatment of multidrug-resistant TB, the first new anti-TB treatment for over 40 years [6]. Unfortunately, bedaquiline has frequent, sometimes serious, side-effects and several drug interactions, further limiting its use. Overall, the track record for drug innovation in respiratory medicine is therefore very disappointing.

The disappointing record of new drug development in respiratory medicine is in contrast to other major therapeutic areas, such as HIV/AIDS, haematology, cardiovascular, dermatology, cancer in general and neurological disease (table 4) [7]. This shows that the cumulative probability of respiratory drugs reaching the market is only 3%, compared to 6–14% for other disease areas. This is despite the fact that many of the new drugs in development are likely to be from existing classes of therapy already in the clinic. The reasons for the higher attrition rate for respiratory drugs needs to be better understood in order to address this issue in the future. The problem is almost certainly multifactorial and there are likely to be several contributory causes, including poor understanding of the underlying disease mechanism, poor animal models for testing new treatments, difficulties of developing drugs for inhaled delivery, and lack of investment in respiratory research and respiratory drug development. For example, although the respiratory market makes up ~25%

TABLE 4 Probability of drugs entering the market for different therapeutic areas

| Area | Drugs n | Market entry probability | | | Cumulative |
|---|---|---|---|---|---|
| | | Phase II | Phase III | Approved | |
| **HIV/AIDS** | 108 | 75 | 50 | 36 | 14 |
| **Dermatology** | 122 | 8 | 44 | 29 | 11 |
| **Haematology** | 163 | 60 | 4 | 22 | 9 |
| **Neurology** | 192 | 73 | 47 | 22 | 8 |
| **Cancer** | 68 | 78 | 46 | 20 | 7 |
| **Cardiovascular** | 280 | 69 | 4 | 22 | 6 |
| **Respiratory** | 165 | 68 | 31 | 16 | 3 |

Data are presented as %, unless otherwise stated. Adapted from [7].

of drug spending, only a small proportion of total research and development funding is allocated to respiratory drug discovery, markedly reducing the identification of novel drug targets.

## The challenges of drug discovery

Very high attrition rates during the process of drug discovery are making it more difficult and more expensive to bring new drugs, particularly new chemical entities, to market. For every approved new drug there are ~10 000 chemicals with a marked loss of compounds at every stage of development (fig. 1). There is a need to markedly improve the efficiency of research and development of drugs [8]. Most of the drugs now approved by the US Food and Drug Administration and the European Medicines Agency (EMA) are in the same class as those already on the market (me-too drugs) or are antibodies with predictable effects, with a falling number of novel classes of drug. Large pharmaceutical companies need to produce several new chemical entities each year in order to grow and this is almost impossible to achieve with current rates of attrition. For example, GSK, a major player in the respiratory field with revenues in excess of $32 billion per annum in 2003, would need to develop approximately six high-quality new chemical entities per year. Of the drugs entering phase I clinical trials between 1991 and 2000, only 11% successfully achieved registration with the greatest drop off occurring in phase II and III studies. Even after registration, ~25% of drugs fail with the full costs of drug development completely lost. The reasons for drug attrition have been carefully analysed with a view to reducing the high wastage of drugs [8]. Before 2000, poor pharmacokinetics and bioavailability were common causes for drug failure. As a result, the industry invested in the development and application of much more accurate prediction and modelling approaches meaning that these are now rarely a cause of failure. Lack of efficacy is now the most common cause of drug attrition and this appears to be a particular problem in respiratory diseases as preclinical animal models are so poorly predictive of the human condition. Between 2011 and 2012, 60% of drugs failed because of lack of efficacy, with 52% failing at phase III and beyond [9]. Improved early proof of concept studies should help to reduce this cause of loss of drugs so that compounds would fail earlier in their course of development and save future costs (quick win, fast fail). Other common causes of failure are safety issues, with 33% of drugs failing for this reason at phase III. This is obviously a much greater risk for small molecule new chemical entities with a novel mechanism of action. There is now less risk of failure for toxicological reasons by eliminating compounds with mechanism-based toxicity; for example, molecules with a particular chemical signature linked to toxicity. Improved toxicity models have also reduced the risk of failure on toxicological grounds. There is a need for better biomarkers to predict drug efficacy and this is a key element in improving the translation from drug discovery to developing a useful clinical treatment [10].

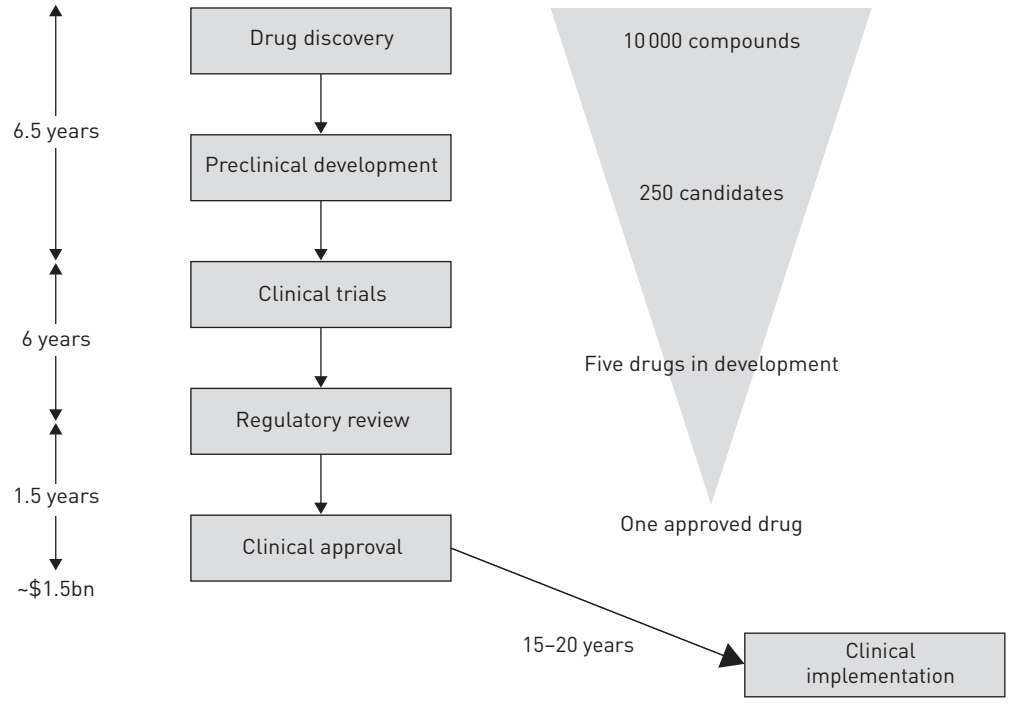


FIGURE 1 Process of drug discovery showing duration and attrition.


DOI: 10.1183/09031936.00007915

The costs of drug development are increasing and it is now estimated that it costs over $1.5 billion to develop each approved drug (at 2011 costs), with costs escalating as the drug progresses further along the development path [7]. The result is that late stage failure during drug development is very expensive and makes it almost impossible for companies to recoup the considerable research and development investment in bringing a drug to market. Reducing attrition, especially late stage attrition, by even a small amount would have a significant impact on the cost of drug development, with complete abolition of attrition reducing the cost of taking a drug to market by almost 80% [11]. The duration for drug development is also getting longer with an overall time from drug discovery to registration of >12 years with approximately 6–7 years in clinical development. The cost for developing respiratory drugs is greater and the duration of development longer than for most therapeutic areas [7].

## Repurposing old drugs

An attractive approach to accelerate drug discovery is to find new uses for existing drugs by screening them against novel targets [12, 13]. This means that if the drug is already on the market it avoids the problems of side-effects, which are often an issue for new chemical entities. Moreover, the pharmacokinetics of these molecules is already established in humans and the time for drug development is markedly shortened. There are several good examples already in clinical practice. Gabapentin, initially developed as an anti-epileptic, has been found to be useful in treating neuropathic pain. Thalidomide, developed as a sleeping tablet, was later found to have immunosuppressive effects and is now used to treat various autoimmune diseases. An example in the respiratory field is sildenafil, originally marketed for erectile dysfunction and now the most broadly used agent for treating pulmonary hypertension worldwide. An example in the broader respiratory area is theophylline, which was originally used as a bronchodilator, an effect mediated mainly through inhibition of phosphodiesterase-3 in airway smooth muscle cells. It has now been discovered that in lower concentrations theophylline has a completely different effect, which is to increase histone deacetylase-2 after it has been reduced by oxidative stress, reversing the corticosteroid resistance induced by oxidative stress [14]. The effect of theophylline is mediated *via* inhibition of phosphoinositide-3-kinase-δ (PI3Kδ), which is reduced by oxidative stress in COPD lungs [15]. Clinical trials are now underway to see if low-dose theophylline combined with low-dose oral corticosteroids or ICS has clinical efficacy in COPD by overcoming corticosteroid resistance. Because this new effect of theophylline is seen at lower doses, the side-effects which previously limited its use as a bronchodilator are no longer a problem.

Drugs for a particular indication may be found to be ineffective during development, but may find uses in another disease area [16]. For example, sildenafil was originally developed for treating angina, but through a side-effect was found to be useful in treating erectile dysfunction. Macrolides were developed as antibiotics but also have anti-inflammatory effects through inhibition of the proinflammatory transcription factor nuclear factor-κB and enhance corticosteroid responsiveness through inhibition of PI3Kδ [17, 18].

The development of high throughput screening techniques has enabled the rapid screening of thousands of new molecules and an interesting application of this approach was a search for unexpected synergy between existing classes of drug [19]. For example, there is an unexpected interaction between corticosteroids and the antiplatelet drug dipyridamole, which enhances the anti-inflammatory effect of corticosteroids in models of arthritis [20]. A similar synergy was discovered between corticosteroids and the tricyclic antidepressant nortriptyline, which enhances corticosteroid responsiveness through inhibition of PI3Kδ, in the same way as theophylline [21]. There may be many more examples of such interactions to be discovered and exploited.

## Better preclinical models of respiratory disease

Many of the new respiratory drugs that have failed in the clinic because of safety and/or efficacy issues have performed well in preclinical animal models. The failure to translate promising drug candidates from animal models to humans has led to questions about the utility of *in vivo* studies and the need for more predictive models and tools based on the latest technologies [22].

A variety of *in vitro* and *in vivo* approaches are used during preclinical drug development. To validate targets of interest early in development, compounds are normally profiled in high-throughput proof of concept studies in human cell-based assays. However, although cell-based assays can provide some information, cultured cell systems do not recapitulate the complex interactions between different cell types and tissues *in vivo*. Furthermore, many cell-based assays utilise transformed cell lines exhibiting different gene expression and cell cycle profiles when compared to primary cells or cells over-expressing various proteins of interest, which again may not behave as they do *in situ*.

Compounds with favourable properties are progressed to *in vivo* animal models to validate the hits identified during high-throughput screening and exclude compounds with unfavourable absorption,

excretion and toxicity properties, which are responsible for >50% of compound attrition in clinical trials. *In vivo* profiling is normally initiated following the lead optimisation stage when a lead compound has been identified. This is mainly due to the high cost and low-throughput of conventional rodent models and the relatively high number of hits from high-throughput screening initiatives.

Lead compounds are selected following this process with the required *in vivo* potency against its target and the desired pharmacokinetic/pharmacodynamic properties *in vivo*. Successful proof of concept studies in animal models that mimic aspects of the human disease pathology/pathophysiology normally precede first time in human studies.

The lack of translation of promising new therapies to the clinic suggests that the tools available to respiratory disease researchers and drug development teams may not be appropriate and a fresh approach should be explored. Current *in vitro* approaches lack complexity and animal models will always struggle to replicate the pathophysiology of uniquely human diseases, such as asthma. The challenge is to develop a suite of complimentary models that more accurately recapitulate human respiratory disease, including the influence of environment and lifestyle on these conditions.

### *Non-mammalian alternative models*

Technological advances in tissue engineering, microfluidics and organ-on-chip approaches are providing researchers with new opportunities for innovative model development and it is essential that the respiratory disease research community embrace these changes. With advances in bioreactor and scaffold technologies, it is now possible to create biomimetic tissue constructs that incorporate multiple relevant cell types cultured at the air–liquid interface and which include a rudimentary circulatory system. Using these systems, researchers are able to better understand the dynamic interplay between static and mobile cells in diseased airways to examine how environmental insults interact with asthma susceptibility genes [23, 24]; and to examine the interaction between cells in the airway wall during airways remodelling [25, 26]. The emerging fields of microfluidics and organ-on-chip are adding further complexity and functionality to tissue engineered constructs and have been used to successfully microfabricate tissues including blood vessels, muscles, brain and liver for basic research and drug discovery [27, 28]. Researchers from the Wyss Institute at Harvard University (Cambridge, MA, USA) have recently created a "breathing" lung-on-chip model that is able to recreate complex organ-level physiological and pathological responses [29]. The immediate application of these systems has been for toxicity testing [30]; however, the potential utility of these models for improving understanding of complex disease processes has been established [31].

Additional opportunities for better understanding the molecular mechanisms of respiratory diseases may also be offered by non-mammalian model systems, including *Caenorhabditis elegans*, *Drosophila melanogaster*, zebrafish and *Dictyostelium*. These models have been widely employed in diverse disease areas including oncology, neurodegenerative disease and ageing. They offer many advantages over more complex vertebrate systems, including genetic amenability, low cost and culture conditions compatible with large scale screens, allowing high-throughput screening in a physiological context.

Despite these advantages, non-mammalian model systems have not, with the exception of a handful of groups, been adopted by the respiratory research community. The lack of lungs and adaptive immune systems (*C. elegans* and *D. melanogaster*) are the most commonly cited reasons for overlooking these model organisms for respiratory disease research. However, numerous biological processes and genes are conserved between these model systems and humans. These include asthma susceptibility genes involved in innate immunity [32, 33], making these model systems attractive options for studying innate immune responses in isolation of an adaptive immune system. The genetic tractability of these organisms, together with the rapidly increasing number of transgenesis tools available, make them ideal models for understanding the role of individual genes, or gene clusters in a disease pathway, identifying putative candidate genes for further downstream functional analysis in other model systems. The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs; London, UK) has recently awarded four research projects focused specifically on pioneering non-mammalian models for asthma research, which will use *Drosophila*, zebrafish and the slime mould *Dictyostelium* to better understand how asthma is triggered and how new treatments may act [34].

### *Improving animal models*

Rodent models have long been used to model respiratory diseases such as asthma and COPD. Some of the defining features of these diseases can be reproduced using various stimuli: allergen, irritant gas exposures, cigarette smoke or exogenous elastase [35]. However, the modelling process is incomplete because the use of single stimuli does not mimic the rather varied and variably timed exposures of subjects and the disease chronicity observed in real life. It is clear that further refinement of current models and biomarker


DOI: 10.1183/09031936.00007915

identification is necessary, and efforts are ongoing in these areas; for example, the development of longer duration chronic models sensitised with more physiologically relevant antigens, modelling of viral/bacterial exacerbations, comorbidities and assessment of disease symptoms. Furthermore, this data should be coupled to human cell and tissue studies and ultimately when phase II ready compounds are available in early proof of concept clinical trials.

Animal models are clearly of importance in pharmacokinetic/pharmacodynamic assessment of lead compounds and in linking efficacy with evidence of target engagement. Their use as models of "disease" needs to be viewed cautiously and in conjunction with translational data generated in human *in vitro* assays and in proof of mechanism studies in normal volunteers. As such, the timely development and application of more predictive *in vitro* and *in vivo* models of respiratory disease, based on the most current knowledge of the human disease, should be considered a priority by the respiratory research community. Greater collaboration between industry, academia, clinicians and regulators is essential to move these aspirations forward and ensure the latest advances are being used to improve the power of respiratory disease modelling and drug development.

## Regulatory aspects of respiratory drugs

Greater collaboration in recent years between academia and the pharmaceutical industry has produced major scientific breakthroughs in the mechanistic, cellular and molecular understanding of respiratory diseases [36]. This has resulted in new translational options for developing innovative therapies for patients with unmet medical needs, but not innovation in the respiratory drug area.

In fact, from a review of all innovative medicines (defined for the purpose of this survey as any chemical, biological or radiopharmaceutical substances not previously authorised as a medicinal product in the European Union) in the period 2010–2013, only eight (5.7%) out of the 141 medicines licensed by the EMA through a centralised procedure referred to respiratory drugs (when cancer and anti-infective drugs were excluded) [37]. This percentage is low when related to the scientific, social and marketing relevance of the respiratory area. For only four of these products innovation was related to a new mechanism of action (ivacaftor in cystic fibrosis, pirfenidone in idiopathic pulmonary fibrosis, roflumilast in COPD and riociguat in idiopathic and thromboembolic pulmonary hypertension). However, the other innovative drugs referred to well-known product classes (*e.g.* the long-acting muscarinic antagonists aclidinium bromide and glycopyrronium bromide), or to a new delivery method or formulation (indacaterol/glycopyrronium and fluticasone furoate/vilanterol, and inhaled prostanoids), or to a well-known substance used in an orphan condition (*e.g.* mannitol in cystic fibrosis).

It should also be noted that marketing authorisation does not necessarily imply that the drug is automatically made available to all European citizens. In fact, at present, none of the above mentioned innovative products are available in all European countries. Even ivacaftor, which obtained marketing authorisation 2 years ago following a very rapid procedure, is available in only 11 European countries.

Why so much is "lost in translation". Clearly, bringing a new medicine to market is a risky, slow and difficult challenge. However, even when marketing authorisation is obtained, Health Technology Assessment (HTA) and decisions on drug pricing and reimbursement at a national (or regional) level can often further delay access to medicines for patients. This bottleneck might become even tighter in the future because of the increasing costs of drugs, particularly biologics. Therefore, as suggested by the World Health Organization report on Priority Medicines for Europe and the World [38], a close collaboration is needed among all drug stakeholders for facilitating early access for patients to innovative drugs.

### *EMA initiatives for innovation*

Several initiatives have been implemented at the EMA to support pharmaceutical innovation and reduce the lag time between marketing authorisation and access to market in all European countries of safe, effective and affordable drugs. These initiatives also have the added benefit of reducing the uncertainty on the outcome of a risky commitment for industry and investors [39].

#### *Adaptive licensing*

This represents a new adaptive approach to marketing authorisation which replaces the "magic moment" of the approval/non-approval decision with a series of approval stages during a continuous evaluation of the drug [40]. In practice, the drug is initially licensed and allowed to enter the market for a restricted population through new study designs, even in small population samples, but without reducing a satisfactory risk:benefit ratio. Authorisation may then be extended to a wider population on the basis of evidence acquired through adequate post-registration studies, the use of registries and the monitoring enabled by the new pharmacovigilance registration. A call for pilot studies on this facilitated pathway for the timely access to drugs (including respiratory drugs) has recently been made by the EMA.

*Joint scientific advice/HTA*

This is based on an early dialogue between regulators and HTA bodies in order to evaluate whether the risk:benefit ratio of a new drug is associated with the added value of an efficient use of resources. At present, 35 procedures of joint scientific advice between the EMA and HTA bodies have been activated for products with indication in several diseases, including asthma and COPD.

*Closer communication among all drug stakeholders*

This has also been recommended by the World Health Organization report [38]. It will hopefully be enhanced by the Health Care Professional Working Parties established at the EMA, in addition to other EMA initiatives to support small to medium enterprises and to make a single, accessible communication channel available for all stakeholders; in particular, biologics, biosimilars, advanced therapies such as stem cell and gene therapies, and stratified medicine require a strict collaboration between academia and regulators for their development and evaluation. Persisting distrust from both sides should be overcome to share experience, joint projects for independent research, education and personnel, possibly with the financial support of Horizon 2020 [41] and the second phase Innovative Medicines Initiative [42] programmes.

*Transparency policy on the pro-active publication of clinical trials data*

The recent EMA transparency policy on the pro-active publication of clinical trials data [43] also represents a valuable source of information for researchers, and may open a new way of collaboration between regulators and academia while respecting the privacy of patient data and commercially confidential information. In fact, re-analysis of data of clinical reports of drugs submitted for marketing authorisation (independently of whether this has been granted, refused or the application has been withdrawn) may increase the existing knowledge, improve further drug research and help regulators to review decisions taken, if needed. The policy has taken adequate measures to avoid commercial use of published information, and the EMA also expects a high ethical behaviour of all who access clinical trial data to avoid inappropriate re-analysis, which may create unjustified concern by patients and healthcare professionals on marketed drugs [44].

The open data policy, as well as the large amount of data emerging from new clinical trial and pharmacovigilance legislations [45], requires appropriate information technology infrastructures for gathering, validating, processing and analysing all the information made available.

Such an "innovation system" seems promising and should be further expanded beyond Europe to involve global players (*e.g.* USA, Japan and emerging economies) in order to reduce disparity in the patient's right to have access to safe, effective and affordable drugs.

## A national model of a respiratory research agency

Confronted with an ageing demographic and an accompanying rise in healthcare costs due to an increasing number of people suffering from major diseases, the German Federal Government initiated its Health Research Framework Program and established six German centres for health research (Deutsche Zentren der Gesundheitsforschung; DZG). Through an innovative structure of partnerships between top universities with university hospitals and non-university research institutions throughout Germany, a key aim of the DZG is the rapid development of new therapeutic options for major public health issues. The first two DZGs, the German Centre for Diabetes Research and the German Centre for Neurodegenerative Diseases, were founded in 2009. Four additional centres followed in 2011: one each for cardiovascular disease, infectious disease, cancer and lung research.

The German Centre for Lung Research (Deutsches Zentrum für Lungenforschung; DZL) has the mission of using "translational research to combat widespread lung diseases". Capitalising on the strong respiratory research competencies that already exist in Germany, the DZL brings together more than 200 principle investigators and their research groups through the establishment of five DZL centres: Airway Research Center North (ARCN), Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Comprehensive Pneumology Center Munich (CPC-M), Translational Lung Research Center Heidelberg (TLRC), and the Universities of Giessen and Marburg Lung Center (UGMLC). Each centre includes several local partner institutions. The scientific and administrative activities of the DZL are coordinated by the DZL head office located at the UGMLC in Giessen, and DZL funds are administered through the funding management office at the Helmholtz Center in Munich.

Research efforts in the DZL are focussed on eight disease areas: asthma and allergy, COPD, cystic fibrosis, pneumonia and acute lung injury, diffuse parenchymal lung disease, pulmonary hypertension, end-stage lung disease and lung cancer. In order to facilitate rapid progress, DZL scientists use an integrated and synergistic approach when researching these disorders. This scientific approach explores the dynamic


DOI: 10.1183/09031936.00007915

relationships among: 1) generation, regeneration and repair; 2) inflammation and resolution of inflammation; and 3) hyper-proliferation (cell cycle control and matrix regulation) across all DZL diseases studied. Thus, discoveries in one disease area are likely to be applicable across several disease areas. In addition to a unified scientific approach, the DZL teams employ a concerted translational strategy to combat these diseases including studies of molecular signatures and pathways in cell and animal models, to clinical trials, disease cohorts, epidemiology and studies of health economics.

In alignment with the DZG philosophy that cooperation and collaboration will serve to facilitate rapid discovery, every disease studied by the DZL engages scientists at three to five of the DZL centres. In addition, many investigators belong to more than one disease area team, allowing for cross-fertilisation of ideas and findings across research areas. Not only are there tremendous synergies across the research programmes in the DZL, but there are synergies with other DZGs as well. Several of the diseases studied by the DZL have mechanistic or even system overlap with those studied by other health centres (*e.g.* pulmonary hypertension, which involves the intimate relationship between the lungs and the heart). Correspondingly, several DZL investigators are faculty members of other DZGs, in particular those focussing on cardiovascular and infectious diseases and cancer.

Central to the success of the DZL translational strategy is access to state-of-the-art research infrastructure which crosses all disease areas. To support and facilitate its translational research efforts the DZL invests in platform technologies to which all DZL researchers have access. These include a DZL-wide biomaterial repository (Biobank), an imaging platform, and a unified data management structure. A technology transfer consortium has been formed to help manage, protect and commercialise DZL findings. In addition, some of the largest lung disease patient and biomaterial cohorts in the world, including CAPNETZ and COSYCONET, are linked with the DZL, allowing access to DZL researchers. Finally, developing the next generation of respiratory translational researchers is central to a sustainable approach and, as such, the DZL has established mentoring and training programmes.

## European Respiratory Society research agency

As part of its new strategic development, the European Respiratory Society is currently exploring the possibility of establishing its own research agency [46]. One of the roles of this agency may be to collect data on different respiratory diseases, including the establishment of a tissue bank for blood, sputum and lung samples and the merging of established cohorts. This may allow better phenotyping of respiratory diseases and may aid the development of biomarkers, which are greatly needed to facilitate drug development in respiratory disease. In future it may be possible for the research agency, in collaboration with pharmaceutical companies, to conduct key clinical trials in well-phenotyped patients and speed up the development of drugs for respiratory diseases, including rare lung diseases, with the contribution of multiple respiratory clinical research centres across Europe.

## Conclusions

Respiratory diseases remain an area of considerable unmet medical need and it is valid to question whether the current approach to drug discovery in this area is sophisticated enough to meet the needs of the industry and patients. The respiratory disease community has recognised the issues and have joined together in instigating a number of changes/initiatives to respond to this.

Clear efforts are being made to understand and address the limitations in the current disease modelling approaches, with greater willingness to move away from the standard "off-the-shelf" historical models to those that directly measure what the candidate molecule is targeting. At the heart of this are global collaborative efforts between academia and the pharmaceutical industry to better understand the human condition through large-scale, well-characterised patient studies, and to integrate this knowledge in the development of more predictive *in vitro* and animal models. The adoption of these new models is being facilitated by a more flexible regulatory framework, better able to respond to and capitalise on advances in knowledge/technology approaches and expedite the exploration of new areas. For this to be truly transformative will require greater harmonisation across regulators globally, but with the successful implementation of initiatives, such as those being driven by the EMA, there is no reason to believe that that this will not translate globally.

Finally, a framework for specific and sustained funding must be encouraged to support collaborative and imaginative research. This has to recognise the importance of supporting cross-disciplinary and -sector researchers, and the next generation of respiratory disease scientists to sustain progress in the development of new and effective therapies for respiratory disease and ensure any mistakes of the past are not repeated.

The European Respiratory Society may be able to facilitate drug development in respiratory medicine in the future through the establishment of a research agency.

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