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COMMENTARY

Mouse models of allergic asthma: acute and chronic allergen challenge

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Asthma is defined as a chronic inflammatory disease of the airways; however, the underlying physiological and immunological processes are not fully understood. Animal models have been used to elucidate asthma pathophysiology, and to identify and evaluate novel therapeutic targets. Several recent review articles (Epstein, 2004; Lloyd, 2007; Boyce and Austen, 2005; Zosky and Sly, 2007) have discussed the potential value of these models. Allergen challenge models reproduce many features of clinical asthma and have been widely used by investigators; however, the majority involve acute allergen challenge procedures. It is recognised that asthma is a chronic inflammatory disease resulting from continued or intermittent allergen exposure, usually via inhalation, and there has been a recent focus on developing chronic allergen exposure models, predominantly in mice. Here, we review the acute and chronic exposure mouse models, and consider their potential role and impact in the field of asthma research.

Disease Models & Mechanisms • DMM

INTRODUCTION

Human allergic asthma is defined as a chronic inflammatory disorder of the airways and is characterised by airway inflammation, persistent airways hyperresponsiveness (AHR) and intermittent, reversible airways obstruction (GINA, 2006; Bousquet et al., 2000). In addition, structural changes in the airway including subepithelial and airway wall fibrosis, goblet cell hyperplasia/metaplasia, smooth muscle thickening and increased vascularity are observed (Bousquet et al., 2000; Fish, 1999). These changes are termed 'airway remodelling' and may be the result of repeated exposure to the allergen, which causes repeated or continuing inflammation in the airways (Zosky and Sly, 2007). Chronic inflammation and structural changes are thought to have functional consequences that contribute to asthma symptoms.

The exact cellular and biochemical processes underlying chronic inflammation and airway remodelling are poorly understood. Although the best approach to investigate these processes, and to identify crucial pathways and potential novel targets for drug therapy, is to perform studies in human asthmatics, the required mechanistic studies are not acceptable owing to ethical reasons. Animal models provide an alternative for investigating disease mechanisms and progression. Because asthma is a complex multifactorial disease, it is unlikely that a single animal model of asthma that replicates all of the morphological and functional features of the chronic human disease will ever be developed. However, we can use animals to model specific features of the disease, and much of our current understanding of disease processes in asthma, and in particular the response to allergens, comes from studies in laboratory animals such as guinea pigs, rats and mice. The mouse is the most widely used species, mainly because of the availability of transgenic animals and because of the wide array of specific reagents that are available for analysis of the cellular and mediator response. This Commentary will, therefore, focus on the development of allergen challenge models in the mouse.

ACUTE ALLERGEN CHALLENGE MODELS

Mice do not spontaneously develop asthma; so, in order to investigate the processes underlying this disease, an artificial asthmatic-like reaction has to be induced in the airways. Mouse models of the acute allergic response to inhaled allergens have been widely used to elucidate the mechanisms underlying the immunologic and inflammatory responses in asthma, and for the identification and investigation of novel targets for controlling allergic inflammation.

A variety of different acute allergen challenge models have been developed in mice and a number of sensitisation and challenge protocols have been employed. Some of these are summarised in Table 1.

The nature of the acute inflammatory model may be influenced by the choice of mouse strain, the allergen, and the sensitisation and challenge protocol (Zosky and Sly 2007; Kumar et al., 2008). The most commonly used strain of mouse for antigen challenge models is BALB/c as they develop a good T helper cell 2 (Th2)-biased immunological response (Boyce and Austen, 2005). However, other strains (C57BL/6 and A/J) have been used successfully in allergen challenge studies (Kumar et al., 2008). Ovalbumin (OVA) derived from chicken egg is a frequently used allergen that induces a robust, allergic pulmonary inflammation in laboratory rodents. A review of OVA challenge models has recently been published by Kumar et al. (Kumar et al., 2008). OVA, however, is seldom implicated in human asthma, and other groups have used alternative allergens that may have greater clinical relevance, for example house dust mite (HDM) and cockroach extracts (Johnson et al., 2004; Sarpong et al., 2003).

Although many different sensitisation and challenge protocols have been used, the basic model is consistent. Acute sensitisation protocols usually require multiple systemic administration of the allergen in the presence of an adjuvant. Adjuvants such as

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Table 1. Mouse models of acute allergic pulmonary inflammation

Gender/strain	Allergen	Sensitisation	Exposure/challenge	Responses to challenge	References
Female BALB/c	OVA	OVA/alum (i.p.) on days 0 and 12	OVA aerosol on days 18-23	From day 24: AHR, increased eosinophils in BAL and lung tissue. Remodelling and Th2 cytokine induction	Lloyd et al., 2000; McMillan et al., 2002; McMillan et al., 2005
Female BALB/c	OVA	OVA + $AlOH_3$ (i.p.) on days 0 and 14	OVA aerosol on days 28-30	From day 32: AHR, increased eosinophils in BAL and lung tissue. Remodelling and Th2 cytokine induction	Tomkinson et al., 2001; Hamelmann et al., 1999a
Male BALB/c	OVA	OVA (i.p.) on 7 alternate days	OVA aerosol for 8 consecutive days (starting on day 27)	24 hours post final OVA challenge: AHR, increased eosinophils in BAL and lung tissue. Th2 cytokine induction	Hessel et al., 1995; Janssen et al., 2000
Female BALB/c	OVA	OVA + alum (i.p.) on days 0 and 14	OVA (i.n) on days 14, 25, 26 and 27	From day 28: AHR and increased eosinophils in BAL and lung tissue. Remodelling	Henderson et al., 1996
Male BALB/c	OVA	OVA (i.p.) on 7 alternate days	OVA (i.t.) on day 42 for 3 days, each 3 days apart	24 hours post final OVA challenge: increased eosinophils in BAL and lung tissue	Blyth et al., 2000
Male A/J	Bla g 2 and Der f 1	OVA + $AlOH_3$ (i.p.) on days 0 and 7	Allergen (oro-tracheal) on day 14	From day 17: AHR (only to Bla g 2) and increased eosinophils in BAL and lung tissue	Sarpong et al., 2003
Male C57BL/6	HDM	Der p 1 + $AlOH_3$ (i.p.) on day 0	HDM (aerosol) on day 14 for 7 consecutive days	AHR and BAL and lung tissue inflammation at 24 hours post final challenge	Tournoy et al., 2000
Female BALB/c	OVA	OVA + alum (i.p.) on days 0 and 14	OVA aerosol on days 28-30 and 72 days after last challenge	AHR and BAL eosinophilia on days 32, 37, 44 and 74	Kanehiro et al., 2001
Male BALB/c	OVA	OVA + $AlOH_3$ (i.p.) on days 0 and 5	2×OVA inhalations, each 4 hours apart on day 17	Following OVA challenge: AHR, EAR and LAR observed	Fernandez-Rodriguez et al., 2008
Male BALB/c	OVA	OVA + $AlOH_3$ (i.p.) on day 0 and OVA i.p. on day 10	OVA aerosol on days 17 and 24	Following OVA challenge: EAR and LAR. Increased inflammatory cells in BAL and lung tissue	Choi et al., 2005

Bla g 2, recombinant *Blatella germanica* 2 (cockroach allergen); Der f 1, *Dermatophagoides farinae* 1 (house dust mite allergen); BAL, bronchoalveolar lavage; EAR, early asthmatic response; LAR, late asthmatic response.

aluminium hydroxide ($AlOH_3$) are known to promote the development of the Th2 phenotype by the immune system when it is exposed to an antigen. Adjuvant-free protocols have also been described (Blyth et al., 1996), but these usually require a greater number of exposures to achieve suitable sensitisation. Sensitisation solely via the airways has also been attempted using both OVA and HDM. With OVA models, success has been limited and only modest pulmonary inflammation and mild AHR have been observed. This might be because tolerance can develop when model protein antigens are delivered via inhalation without systemic sensitisation. Inhaled delivery of HDM has been more successful, possibly because of the intrinsic enzymatic activity of this allergen. After the sensitisation period (usually 14-21 days), the animal is challenged with the allergen via the airway, usually over a period of several days. Allergen may be inhaled as a nebulised formulation (aerosol), or administered by intratracheal (i.t.) or intranasal (i.n.) instillation of an aqueous formulation.

The acute challenge mouse models reproduce many key features of clinical asthma, for example elevated levels of IgE, airway inflammation, goblet cell hyperplasia, epithelial hypertrophy, AHR to specific stimuli and, in some models, early- and late-phase bronchoconstriction in response to allergen challenge. However, there are also some major differences. In acute challenge models, the pattern and distribution of pulmonary inflammation is different from that observed in individuals with asthma (Kumar and Foster, 2002). For example, bronchoalveolar lavage and histology studies indicate that the influx of inflammatory cells is dominated by eosinophils. Because of the short-term nature of the acute models, many of the lesions observed in chronic human asthma, such as chronic inflammation of the airway wall, and airway remodelling changes are absent. Furthermore, many of the key features appear to be short-lived and, in some models, airways inflammation and AHR have been shown to resolve within a few weeks after the final allergen challenge (McMillan and Lloyd, 2004).

Despite these apparent shortcomings, acute allergen challenge models have been successfully used to investigate disease processes, in particular the relationship between cells and inflammatory mediators, and how they orchestrate the inflammatory processes in the lung. Evidence supporting the hypothesis that asthma is a Th2-mediated disease, the role of the T cell in the allergic response, and the role of the eosinophil and its involvement in the development of AHR came from studies in the acute challenge models.

A wide range of cellular and molecular targets have been identified, and subsequently evaluated, in the acute challenge models. These include anti-cytokine approaches, specific mediator antagonists, monoclonal antibodies and specific enzyme inhibitors. With a number of these targets, efficacy has been demonstrated in the acute challenge models, but not in clinical trials in patients. Anti-IL-5 therapy is one of the most frequently discussed examples. IL-5 appears to have a key role in allergen-induced inflammatory responses and the development of AHR in mice. IL-5 knockout mice were protected both from acute allergic inflammation, AHR (Foster et al., 1996) and chronic airway remodelling (Cho, et al.,

Table 2. Mouse models of chronic allergic pulmonary inflammation

Mouse gender/ strain	Allergen	Sensitisation	Exposure/challenge	Responses post final allergen challenge	Reference
Female BALB/c	OVA	OVA + alum (i.p.) on days -7 and -21	OVA for 6/8 weeks (3 days/week)	Intraepithelial eosinophilia, infiltration of lamina propria by mononuclear cells, remodelling, Th2 cytokine induction and AHR	Temelkovski et al., 1998
Female BALB/c	OVA	OVA + alum (i.p.) on days 0 and 14	OVA (i.n.) on days 14, 27, 28, 47, 61 and 73-75	Eosinophilic and mononuclear cell inflammation; goblet cell hyperplasia and mucus occlusion of airways; widespread deposition of subepithelial collagen	Henderson et al., 2002
Female BALB/c	OVA	OVA + aluminium potassium sulphate (i.p.) on days 1 and 11	OVA (i.n.) on days 11, 19, 20, 33, 34, 47, 48, 61, 62, 75, 76, 89 and 90	Increased eosinophilia, remodelling, Th2 cytokine induction and AHR	Leigh et al., 2002a
Female BALB/c	OVA	OVA + alum (i.p.) on days 0 and 12	OVA aerosol on days 18-23 and then 3 days/week for 5/8 weeks starting on day 26	Inflammation, remodelling, Th2 cytokine induction and AHR; TGF-β induction	McMillan et al., 2005
Female BALB/c	HDM extract	–	HDM (i.n.) 5 days/week for up to 7 weeks	Eosinophilic inflammation, remodelling, Th2 cytokine induction and AHR	Johnson et al., 2004
Female BALB/c	HDM extract	–	HDM (i.n.) 5 days/week for up to 5 weeks	Eosinophilic inflammation, lung tissue inflammatory gene expression	Ulrich et al., 2008
Male BALB/c	OVA	OVA + $AlOH_3$ on days 0 and 5	OVA aerosol, starting day 17, 3 days/week for 6 weeks	Eosinophilic inflammation, AHR, and early and late asthmatic responses	Fernandez-Rodriguez et al., 2008
Female BALB/c	OVA	OVA and alum (s.c.) on days 0, 7, 14 and 21	OVA (i.n.) on days 27, 29 and 31, and then twice a week for 3 months	Eosinophilic inflammation, remodelling and TGF-β induction	Lee et al., 2008

2004). However, IL-5 antagonists have been evaluated in both mild acute and chronic severe asthma, and have failed to show clinical benefit (Leckie et al., 2000; Kips et al., 2003). There are other examples of drugs that have shown efficacy in acute challenge models but not in clinical studies; these include VLA4 antagonists (Norris et al., 2005), PAF antagonists (Hozawa et al., 1995) and IL-4 antagonists (Riffo-Vasquez and Spina, 2002; Borish et al., 1999). One possible explanation for the contrasting data from the mouse and human studies is that in mouse acute challenge models it is only possible to assess the affect on the development of allergic responses; whereas with clinical studies, potential suppression of established inflammatory disease is investigated.

Thus, although the acute challenge models have been useful for investigating the process underlying acute airway inflammation and AHR, there are concerns relating to the suitability of acute challenge models for both the investigation of disease processes associated with chronic asthma, and assessing potential novel treatments that may slow, or reverse, the changes of airway inflammation and remodelling, and its effect on lung function.

CHRONIC ALLERGEN CHALLENGE MODELS

In order to address some of the issues associated with acute challenge models, several research groups have investigated chronic allergen exposure in mice. The key aims were to reproduce more of the features of clinical asthma, such as airway remodelling and persistent AHR, and to enable novel therapies to be evaluated in a therapeutic setting rather than a prophylactic setting, i.e. evaluating the effect of a novel drug in an established pulmonary inflammation setting. A number of different chronic challenge models have been developed by increasing the number of allergen challenges, some examples are shown in Table 2. Kumar et al. and Lloyd have discussed some of these models in recent review articles (Kumar et al., 2008; Lloyd, 2007).

Chronic allergen challenge models involve repeated exposure of the airways to low levels of allergen for periods of up to 12 weeks. Different allergens have been employed and co-administration of an adjuvant is not always required. A number of investigators, for example Temelkovski et al., Fernandez-Rodriguez et al. and Wegman have used OVA to establish a chronic exposure (Temelkovski et al., 1998; Fernandez-Rodriguez et al., 2008; Wegmann, 2008). Others have used environmentally relevant allergens such as HDM extract or grass pollen (Johnson et al., 2004; Kim et al., 2006). One anticipated problem with chronic allergen exposure, in particular with model protein antigens such as OVA, was that long-term challenge might lead to the development of tolerance and downregulation of inflammation and AHR (Jungsuwadee et al., 2004; Kumar et al., 2008). Both the strain of mouse and route of allergen administration are factors that may influence the induction of tolerance (McMillan and Lloyd, 2004; Shinagawa and Kojima, 2003). Kumar et al. suggested that tolerance might be related to the high mass concentrations of the aerosolised allergen used, which could overwhelm the clearance mechanisms (Kumar et al., 2008). This group successfully developed a model in which sensitised animals were exposed to inhalation of controlled mass concentrations of aerosolised antigen to minimise parenchymal inflammation and tolerance.

Chronic allergen exposure in mice has been shown to reproduce some of the hallmarks of human asthma including allergen-dependent sensitisation, a Th2-dependent allergic inflammation characterised by eosinophilic influx into the airway mucosa, and

Table 3. Compounds developed, or in development, for the treatment of respiratory disease: profile in preclinical mouse models and in clinical studies

Compound class/mechanism	Profile in acute model	Reference	Profile in chronic model	Reference	Profile in clinical studies	Reference
Corticosteroid (dexamethasone, budesonide, FP)	Inhibited inflammation, AHR and subepithelial fibrosis	Blyth et al., 2000	Inhibits airway inflammation and remodelling	Kumar et al., 2003	Improved lung function (FEV_1) and caused significant improvement in asthma symptom scores	Pearlman et al., 1997
			Inhibited AHR, pulmonary inflammation and ameliorated remodelling	Yang et al., 2005	Attenuated the maximal, late asthmatic response and protected against AHR and sputum eosinophilia	Leigh et al., 2002b
Calcineurin inhibitor (cyclosporine A)	Attenuated BALF eosinophilia and inhibited AHR	Nagai et al., 1996	Inhibited eosinophilia in BAL and lung; AHR was also attenuated	Lee et al., 2006	Increased morning PEF; improved FEV_1 and reduced exacerbations	Alexander et al., 1992
Thromboxane antagonists	Reduced total cell numbers and eosinophils in BALF	Shi et al., 1998	No published data	–	No significant improvement in FEV_1	Stenton et al., 1992
	Partially blocked the induction of AHR	Richter et al., 2007				
Platelet activating factor (PAF)	PAF-acetylhydrolase reduced airway eosinophilia, mucus hypersecretion and AHR	Henderson et al., 2000a	No published data	–	PAF antagonist did not protect against antigen-induced early- and late-phase response	Townley et al., 1994
5-lipoxygenase (Zileuton)	Blocked airway mucus release and infiltration of eosinophils into airway; no effect on AHR	Henderson et al., 1996	No published data	–	Reduced corticosteroid requirement, improved FEV_1 and improved quality of life	Israel et al., 1996
Leukotriene antagonist (Montelukast)	Reduced airway eosinophilia and AHR	Eum et al., 2003	Reduced airway eosinophilia, mucus plugging, smooth muscle hyperplasia and subepithelial fibrosis	Henderson et al., 2002	Improved FEV_1; reduced β-agonist use and nocturnal awakenings	Reiss et al., 1996
Anti-IgE	Reduced OVA-specific IgE, no effect on eosinophilia in BAL or lung, no effect on AHR	Hamelmann et al., 1999b	No published data	–	Reduced exacerbations and steroid and β-agonist use	Busse et al., 2001
					Reduced use of rescue medication; improved asthma-related symptoms; reduced steroid use and improved quality of life.	Holgate et al., 2004
					Improved FEV_1 and morning PEF; reduced exacerbation rate.	Humbert et al., 2005
Anti-IL-5	Inhibited eosinophilia, lung inflammation and AHR	Hamelmann et al., 1999a	Inhibited eosinophilic inflammation and remodelling but had no effect on AHR	Kumar et al., 2004b	Prevented blood eosinophilia but had no effect on LAR or AHR to histamine	Leckie et al., 2000
Anti-IL-4	IL-4 receptor antagonist reduced airway eosinophilia and AHR	Tomkinson et al., 2001	IL-4$^{-/-}$ mice protected from AHR and aspects of remodelling	Leigh et al., 2004a	Soluble IL-4R attenuated drop in FEV_1 and inhibited increase in asthma symptom score	Borish et al., 2001
	Soluble IL-4 receptor reduced inflammation and mucus hypersecretion; no effect on AHR	Henderson et al., 2000b				

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Disease Models & Mechanisms ● DMM

Table 3. Continued

Compound class/mechanism	Profile in acute model	Reference	Profile in chronic model	Reference	Profile in clinical studies	Reference
Anti-IL-13	Soluble IL-13 receptor suppressed AHR	Leigh et al., 2004b	Suppressed pulmonary inflammation; partially suppressed changes in remodelling and had limited effect on AHR	Kumar et al., 2004b	Human anti-IL-13 monoclonal antibody inhibited allergen-induced EAR and LAR	Gauvreau et al., 2008
			Soluble IL-13 receptor had no effect on AHR or remodelling	Leigh et al., 2004b	IL-4 mutein targeting inhibition of IL-4 and IL-13 reduced the FEV1 decreases in response to allergen challenge	Wenzel et al., 2007
VLA-4	Anti-VLA-4 antibody prevented changes in R_L and inhibited cell infiltration in BAL	Kanehiro et al., 2000	No published data	–	Antagonist had no effect on EAR or LAR; no effect on AHR	Ravensberg et al., 2006
Phosphodiesterase -4 inhibitor (rolipram, roflumilast)	Prevented changes in R_L and C_{dyn}, and reduced inflammation, goblet cell hyperplasia and IL-4 and -5 levels in BALF	Kanehiro et al., 2001	Inhibited eosinophil infiltration and ameliorated remodelling; AHR was slightly reduced	Kumar et al., 2003	Inhibited both EAR and LAR	Van Schalkwyk et al., 2005
					Attenuated AHR and reduced the decrease in FEV_1 during late asthmatic response	Louw et al., 2007
Anti-CD4/8	Anti-CD4/8 treatment inhibited AHR and inflammation	Leigh et al., 2004c	Anti-CD4/8 treatment did not inhibit AHR in chronic protocol; remodelling was unaffected	Leigh et al., 2004a	High dose anti-CD4 monoclonal antibody associated with an improvement of PEF; FEV_1 was unchanged from placebo control; non-significant improvement in symptom score	Kon et al., 1998
			Inhibited AHR, remodelling and lung plasma cells; moderate reduction in inflammation; no reduction in intraepithelial eosinophilia and eotaxin expression	Foster et al., 2002		
Anti-TNF-α	Reduced BAL neutrophilia and BAL/lung eosinophilia; BALF cytokines reduced	Deveci et al., 2008	No published data	–	Improved asthma symptoms, lung function and bronchial hyperresponsiveness.	Howarth et al., 2005
	Inhibited late asthma response without affecting early response; reduced airway eosinophilia and inflammation	Choi et al., 2005				

BALF, bronchoalveolar lavage fluid; BAL, bronchoalveolar lavage; R_L, lung resistance; C_{dyn}, dynamic compliance; PEF, peak expiratory flow; EAR, early asthmatic response; LAR, late asthmatic response; FEV, forced expiratory volume.

AHR. In addition, in some models, there is evidence of airway remodelling with goblet cell hyperplasia, epithelial hypertrophy, and either subepithelial or peribronchiolar fibrosis. Importantly, some of the key features of the chronic allergen exposure models have been shown to persist after the final challenge. After cessation of allergen challenge, some features of airway remodelling have been shown to persist in a number of models (Johnson et al., 2004; Macmillan and Lloyd, 2004; Kumar et al., 2004a). In these models, the persistence of AHR and lung inflammation varies depending on the exposure protocols employed (Lloyd, 2007).

There are limitations associated with the chronic models. In some cases, features peculiar to the mouse are observed that are not seen in human asthma. For example, in the mouse, inflammation is not restricted to the conducting airways, whereas it is in humans, and both lung parenchymal and vascular inflammation/remodelling are observed (Wenzel and Holgate, 2006). Large increases in airway smooth muscle, which is a characteristic feature of chronic asthma (Carroll et al., 1993), either does not appear to occur (Wenzel and Holgate, 2006) or, if it does, only after high level challenge (Shinagawa and Kojima, 2003; McMillan and Lloyd, 2004). Furthermore, there is little or no recruitment of mast cells into the airway wall or epithelium (Boyce and Austen, 2005), which may reflect the paucity of mast cells in the airways of mice (Kumar and Foster, 2002).

Despite these issues, using repetitive allergen provocation in mice has been shown to mimic important features of the human disease and would appear to represent an improvement over the acute challenge models.

IMPACT OF CHRONIC ALLERGEN CHALLENGE MODELS ON ASTHMA RESEARCH

Chronic allergen exposure in mice appears to now be the model of choice for studying the role of specific cell types and inflammatory cytokines and mediators in the processes involved in chronic inflammation and, in particular, some of the structural changes to the airways. For example, Humbles et al. have used a chronic challenge model to investigate the role of the eosinophil in airway remodelling (Humbles et al., 2004), and Kumar et al. and McMillan et al. have investigated the role of TGF-β in the development of airway remodelling in their chronic challenge model (Kumar et al., 2004a; McMillan et al., 2005). In addition, Yang et al. have used chronic models to investigate the role of IL-13 in regulating chronic inflammatory changes to the airway (Yang et al., 2005). These, and future, studies will add to our understanding of the mechanisms of chronic inflammation and airway remodelling and their contribution to asthma symptoms.

Chronic models may also provide a more suitable system for the preclinical evaluation of novel therapeutic agents. Unlike acute challenge models, the chronic challenge model enables investigations to be carried out in a setting of established airway inflammation and AHR and, therefore, more closely reflects most of the experimental studies undertaken in the clinic. A number of groups are using chronic models to profile established and novel pharmacological treatments for asthma. These studies might provide an insight into the predictive nature of the chronic models with regard to clinical outcome. A summary of some of the compounds that have been evaluated in mouse acute and chronic allergen challenge models and in human asthma trials is provided in Table 3. A number of anti-inflammatory agents are being profiled in chronic models, and reports of efficacy with corticosteroids (Macmillan et al., 2005), leukotriene receptor antagonists (Henderson et al., 2002) and phosphodiesterase 4 (PDE4) inhibitors (Herbert, et al., 2008) are emerging. Preliminary data suggest that certain chronic models might reproduce sensitivity to drug therapy in the clinic. However, further studies using a wider range of molecules, including examples that have demonstrated positive and negative outcomes in the clinic, are required. These studies will enable investigators to judge whether the chronic models might better reflect clinical outcome and represent an improvement over the acute challenge models.

CONCLUSIONS

Mouse allergen challenge models are a basic, and frequently used, tool for asthma research. Because of the complexity and diverse nature of the disease, it is unlikely that a mouse model that is truly representative of clinical asthma will be developed. Efforts are focusing on modelling specific disease phenotypes rather than trying to reproduce all features of asthma in a single model. Acute allergen challenge models have been extensively used to investigate pulmonary inflammation and AHR, but their use is limited, in particular when relating findings to chronic asthma. Chronic allergen challenge models appear to reproduce some of the features of chronic asthma and might enable key questions, relating to both the pathogenesis of asthma and potential approaches to novel therapy, to be addressed. Both acute and chronic allergen challenge models have limitations that need to be taken into account when extrapolating findings from the animal model to the human disease.

It is important that mouse models are valid and reflect clinical asthma as closely as possible. Studies are ongoing to refine and improve existing models in order to enhance their utility. For example, asthma exacerbations account for the majority of asthma-related hospital visits and this is becoming a focus of research. Mouse models are being developed to model asthma exacerbations, and investigators are using acute and chronic allergen challenge models as a background for superimposing additional, higher intensity allergen challenge (Siegle et al., 2006; Ito et al., 2008) or viral infection (Bartlett et al., 2008).

A combination of improved animal models, which more closely reflect asthma, and use of relevant human systems will broaden our knowledge of the disease and help identify and evaluate new therapeutic targets.

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COMPETING INTERESTS
The authors declare no competing financial interests.

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