Drug development strategies for asthma: in search of a new paradigm

Patrick G Holt[1], Peter D Sly[1], Fernando D Martinez[2], Scott T Weiss[3], Bengt Björkstén[4], Erika von Mutius[5] & Ulrich Wahn[6]

The spiraling costs of asthma treatment seem set to continue rising, given the equivocal performance of the latest generation of specific anti-inflammatory drugs in trials in adult asthmatics. We argue that the continuation of this trend is inevitable unless there is a substantial realignment of entrenched drug development policy in the pharmaceutical industry and a parallel shift in licensing policy by regulatory authorities to encourage the development of drugs capable of halting the progression from acute to chronic asthma when the disease first manifests in childhood. The theoretical framework for such an approach, including proof-of-principle data from studies in children with early-stage disease and a range of candidate drugs, already exists. What is needed is informed debate on the risks versus potential benefits of this approach.

Asthma-like syndromes represent the most frequent cause of hospitalization in pediatric populations in First World countries and are an increasingly important cause of morbidity among adults. The economic effect of these diseases is very high and is increasing. In 1996, 17 million Americans, with approximately one third of those being children, were affected by asthma. The economic burden of asthma in the USA is also increasing, from an estimated US$6.2 billion in 1990 to US$12.7 billion in 1998 (ref. 1). These costs include direct medical costs (58%) as well as indirect costs (42%) such as school days lost, loss of work, housekeeping and mortality.

Initially identified as a post-1960s 'epidemic' in developed countries, the upsurge in asthma prevalence is now also becoming evident in emerging Second World countries transiting to First World economic status and in rapidly developing countries in the Third World. The prevalence of asthma has increased in Bangalore, India, a city known for its high asthma prevalence, from 9.0% of the pediatric population in 1979 to 29.5% in 1999 (ref. 2). Similar trends are reported from other parts of India and from other developing countries in the Asian region, such as China. Based on prevalence rates at present and projected increases, we estimate that the total asthmatic population in India will reach approximately 250 million by 2013, with 80 million in the pediatric age range. Similar projections for China put the future asthmatic population at 150 million, including 38 million children.

These findings represent considerable challenges for public health research, as they indicate that environmental factors related to 'the modern lifestyle' are driving the changes in disease prevalence. They also pose a considerable challenge to the pharmaceutical industry. The spiraling prevalence of asthma, which is most evident in the First World countries with the highest rates of use of newly developed anti-asthma drugs, tells a tale that transcends the need for statistical analysis: the modern generation of drugs may be useful for treating asthma symptoms, but they do not provide a long-term solution to the problem of progressively increasing disease rates.

Drug strategies for asthma at present are based on the premise that disease symptoms derive directly and immediately from airway inflammation. The traditional pharmaceutical approach to asthma treatment has accordingly focused on development of potent anti-inflammatory drugs, particularly steroids that show broad-spectrum inhibitory activity against a wide range of effector cells and their products. However, concerns relating to the potential side effects of steroids and the necessity for their continuous use in chronic asthma have propelled a multi–billion dollar search over the last two decades for drug targets in the inflammatory cascade that are more specific. This has culminated in a recent series of clinical trials of a new range of specific inhibitors for effector mechanisms associated with T helper type 2 (T_H2)–polarized immunity, notably recombinant interleukin 12 as well as antibodies to interleukins 4 and 5 and immunoglobulin E. Although these agents have proven highly effective in antagonizing their respective molecular targets, and in some cases have shown substantial clinical efficacy in

Patrick G. Holt and Peter D. Sly are with the Telethon Institute for Child Health Research, and Centre for Child Health Research, The University of Western Australia, Perth, Western Australia. Fernando D. Martinez is at the Arizona Respiratory Center, University of Arizona, Tucson, Arizona, USA. Scott T. Weiss is in the Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. Bengt Björkstén is in the Centre for Allergy Research and Department of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. Erika von Mutius is at the Dr. von Hauner Children's Hospital, University of Munich, Munich, Germany. Ulrich Wahn is at the University Hospital Charite-Virchow, Berlin, Germany. e-mail: patrick@ichr.uwa.edu.au

syndromes such as allergic rhinitis, they have failed to meet expectations in asthma, in particular in relation to modulation of airway hyperresponsiveness. At present, the indications are that further development of one or more of these T_H2 antagonists is likely to be discontinued, possibly permanently, and if this is the case it is likely to color future drug development decisions relating to immunological targets relevant to a range of inflammatory diseases.

Key elements in the research and development process that has led to the recent trials of these drugs are flawed. In particular, selection of drug targets has relied heavily on acute disease models in animals, which focus on inflammatory mechanisms linked to manifestations of established asthma in human adults. This approach fails to take into account mounting evidence indicating that complex diseases such as asthma arise through multistep processes, with discrete risk factors being operative at proximal versus distal stages of pathogenesis. In the specific case of asthma, the symptomatology of established disease seems to be the result of adaptive changes that occur progressively in airway tissues as a consequence of prolonged inflammation[3]. Thus, treatment of established asthmatics with anti-inflammatory agents (regardless of specificity or potency) could be predicted to have limited efficacy beyond provision of symptomatic relief. Of particular note is the fact that the airways of most established asthmatics become hyper-responsive to a broad range of environmental irritants, some as innocuous as exercise or cold dry air, suggesting that the relative importance of T_H2-mediated inflammatory mechanisms in the maintenance of persistent asthma may diminish with time.

Initiation: developmental factors

The two central elements in the complex asthma equation are the respiratory system and the immune system. Their interactions in established asthma have been studied in detail over many years and the results of these investigations have provided the basis for approaches at present to treatment and drug discovery. Asthma pathogenesis is viewed as the result of interactions between environmental stimuli and a variety of 'susceptibility' genes influencing aspects of immune and respiratory function. However, although the prevailing 'gene environment' paradigm (**Box 1a**) provides a valid framework for the systemic study of asthma pathogenesis, it does not adequately describe events in the initiation of asthma in childhood, as it does not take into account the central importance in disease etiology of the developmental context in which these interactions occur. An alternative view that emphasizes the key denominator function of age-dependent developmental processes in the initiation of asthma (**Box 1b**) is based on a series of recent observations relating to postnatal maturation of respiratory and immune functions, which are summarized below.

Postnatal 'programming'

The presence of asthma-like wheezing symptoms in early life is the result of complex interactions between developmental factors related to the physical dimensions of the airways and factors relating to susceptibility to both infectious disease and allergic sensitization[4]. Clear definition of these interactions is central to understanding how persistent asthma develops. The approach that is proving most productive for this involves large-scale resource-intense prospective cohort studies[5] involving tracking of populations of individual children over a period of years from first manifestation of infant wheezing through to the development of persistent asthma. The information emanating from these studies is progressively reshaping perceptions of how the disease develops and in the process is challenging established clinical treatment and drug development paradigms.

It is now apparent that much of the wheezing in the immediate postnatal period is related to small airway diameter and is accordingly transient[6]. However, episodes of wheezing as a result of lower respiratory tract illness occurring later in infancy have potentially longer-term sequelae. The most important of these involve viral infections, which are responsible for most hospitalizations for bronchiolitis during the first 2–3 years of life. These early infections are associated with notably increased risk for the subsequent development of asthma, which persists for up to 10 years[6] and in some cases may last into adulthood. Sensitization to inhalant allergens is also an important cause of wheezing during infancy[7] and increases the risk of subsequent development of asthma, which persists to (at least) the end of the preschool years[5]. The contribution of allergy to the risk of subsequent asthma seems inversely related to the age at which allergic sensitization initially manifests[8,9], further reinforcing the view that the respiratory system is particularly susceptible to inflammatory damage during early life. The 'worst-case scenario' involves dual early exposure to both classes of inflammatory stimuli, as shown in prospective cohort studies demonstrating that airway damage due to wheezing from multiple lower respiratory tract illness and episodes of respiratory allergy during early childhood interact synergistically to substantially increase the risk of subsequent development of persistent asthma[10].

BOX 1

a. Asthma pathogenesis

Gene environment → Disease

b. Asthma aetiology

Gene environment → Disease
Development

The mechanisms by which early airway inflammation amplifies asthma risk are incompletely understood, but plausible explanations are emerging. In particular, it is known that the lung undergoes profound changes during infancy driven by rapid growth and differentiation, establishing structure-function relationships that are central to respiratory health throughout the rest of life[11]. It has been hypothesized that inflammatory damage during this critical period may initiate phenotypic changes in lung tissues, which are amplified during subsequent growth, eventually culminating in the development of the persistent airway hyper-responsiveness, the hallmark of chronic asthma[10]. In support of this idea, infants who develop low lung function are likely to continue to 'track' at the low end of the functional range as they grow over the next few years and will potentially continue on the same trajectory into adult life[12].

'Imprinting' memory in infancy

'Programming' of T cell memory against the environmental allergens that are recognized as potent triggers of asthma in later life also occurs mainly during this same period and in most children is completed by the age of 5–6 years[10]. Quantitative and qualitative aspects of this process are governed by developmental factors associated with the transition of the immune system from the T_H2-biased state characteristic of the normal fetus to the more balanced T_H0-like state typical of postnatal life. This maturation process involves selective upregulation of T_H1 functions, triggered by contact between the innate immune system and microbial stimuli not present in the fetal compartment, particularly the normal commensal flora of the gastrointestinal tract[10,13]. Airborne microbial breakdown products such as bacterial lipopolysaccharide, which is ubiquitous throughout the natural environment, may also have a stimulating function in this present context[14]. Genetic risk for allergic sensitization during early life is associated with attenuated postnatal maturation of T_H1 function[15], possibly as a result of variations in key pattern-recognition genes such as *Cd14* (ref. 16) and *Tlr2* (ref. 17) and is also likely to involve developmental deficiencies in associated innate immune function.

T_H1 immunity is also prominent in resistance to viral infection and, accordingly, it is plausible that the developmental deficiencies and underlying genetic variations described above for the risk of allergic sensitization may confer comparable risk of respiratory infection and its spread to the lower airways[10]. Indirect evidence in support of this possibility has been provided by several studies in the mouse[18] and in human infants[10], and this may underlie the synergy noted above between wheeze-inducing lower respiratory tract illness and atopy in relation to asthma pathogenesis. Virus infections remain important triggers of severe asthma exacerbations into the teen years but mainly in atopic asthmatics[19], suggesting that underlying atopy itself (or the mechanisms responsible for establishment of the atopic state) create sensitivity to the asthmatogenic effects of infections.

In summary, there is compelling evidence that key events in the developing immune and respiratory systems that ultimately lead to the development of a substantial proportion of persistent asthma occur in a specific 'time window' during early life (**Fig. 1**, Initiation phase) and these are related to inflammatory episodes triggered by inhalation of proinflammatory stimuli such as viruses and aeroallergens. The long-term sequelae of these events involve altered differentiation and subsequently altered structure and function(s) of lung and airway tissues, including hyper-responsiveness to a wide range of nonspecific irritant stimuli (**Fig. 1**, Chronic asthma). It is understandable that these changes are not readily reversible, given the nature of the structural alterations in the asthmatic lung, particularly once the disease enters its chronic phase[3]. The development of effective treatment modalities for this group of asthmatics remains a principal challenge for the pharmaceutical industry. However, an equally important and potentially less formidable challenge also exists: to reduce the incidence of new cases.

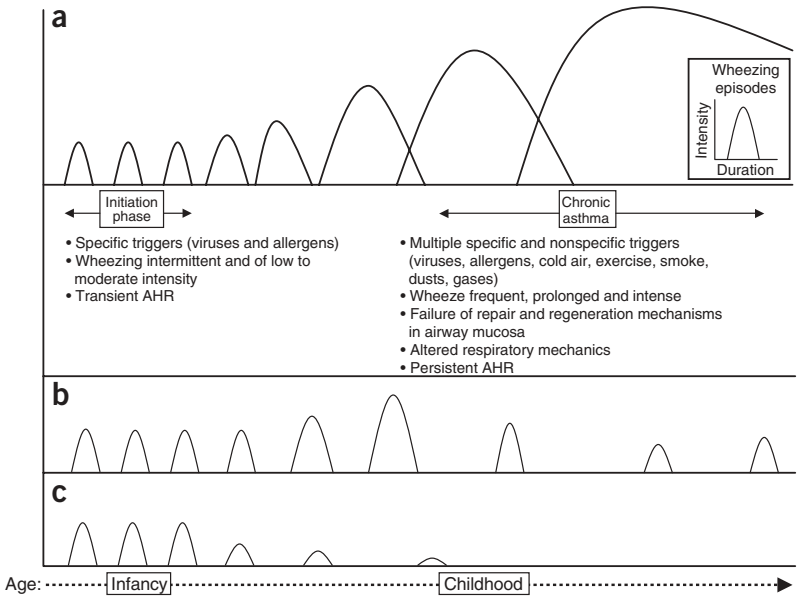

Figure 1 Blocking the progression of intermittent infant wheezing to persistent asthma: protection of airway tissues during critical growth and differentiation in early childhood. (**a**) Infants and young children experiencing repeated wheezing episodes are given symptomatic treatment only, resulting in inflammation-mediated interference with normal lung growth and differentiation and progression to chronic asthma in which exacerbations are triggered by a wide range of environmental irritants. AHR, airway hyper-responsiveness. (**b**) Effective drug treatment results in successful protection of the growing airway from wheeze-associated inflammatory damage and, as a result, wheezing remains sporadic and low to moderate in intensity, triggered mainly by allergy and viral infection. (**c**) Successful protection of the growing airway from wheeze-associated inflammatory damage is coupled with successful desensitization to inhalant allergens, or sensitization does not occur, and wheezing progressively decreases.

Prevention: a realistic short-term target?

Although asthma in childhood consists of several different subtypes, the type of asthma that persists into adult life seems to be typically associated with atopy[8,20,21]. Once this type of asthma has become established, treatment protocols at present are essentially aimed at controlling and containing the disease. An alternative approach, which is attracting increasing attention in the academic medical community, involves intervention much earlier to prevent progression of the disease beyond the stage of mild allergy.

The initial efforts in this direction have focused mainly on prevention of allergic sensitization through allergen avoidance. Results so far have generally been disappointing despite intrusive and difficult-to-maintain regimens, including stringent allergen avoidance during pregnancy and breast-feeding. However, intervention strategies targeted at 'downstream' events in the disease process have shown more promise. These strategies include allergen avoidance through environmental controls aimed at reducing amounts of indoor aeroallergens, which can reduce symptoms in atopic children[7], although the complexity of such measures limits their general applicability. Interventions that are more targeted and focus on specific allergens may be more practical. In particular, specific immunotherapy against pollen given to children 6–12 years of age (the Preventive Allergy Treatment study) has proven successful in decreasing the risk of progression from allergic rhinitis to atopic asthma[22]. Prophylactic forms of immunotherapy targeting high-risk children in young age groups are also feasible[23], and the development of a clinical trial strategy to test this last approach is in progress.

A critical time window exists in early life during which environmental exposures result in an increased risk of allergic sensitization and development of persistent asthma later in life[10,24,25]. Furthermore, allergic sensitization itself is generally not sufficient to produce persistent asthma and additional inflammatory insults (such as viral lower respiratory illnesses in early life) are also required[10]. So far it is not known precisely how wide the critical window of susceptibility may be, nor is it known whether the width of the window varies for different atopic diseases or for different asthma phenotypes. The data from the Preventive Allergy Treatment study[22] suggest that, at least for children with relatively mild nonwheezing atopic disease, this window may extend to between 6 and 12 years of age. However, those with atopic asthma that is more severe in adolescence have generally had symptoms dating from the first year of life, which suggests that the window may be narrower for children at highest risk for severe disease. Large-scale longitudinal birth cohort studies are now in progress at several large pediatric respiratory centers, and these should supply a range of new information relevant to the identification of appropriate target groups for early intervention therapies and the likely time frames of respective treatment windows.

Prophylactic options: where to begin?

The first objective of early treatment for asthma is to provide acute symptomatic relief. However, a second objective is potentially more important for the long-term respiratory health of these children: to minimize inflammatory damage to growing lung and airways, which can deleteriously affect ongoing differentiation of these tissues, precipitating the phenotypic changes, ultimately resulting in persistent asthma (**Fig. 1a**). The potential outcome of successful early treatment with appropriate anti-inflammatory drugs (**Fig. 1b**) is that wheezing in these children will remain of low to moderate intensity and sporadic. An important caveat is that such treatment should not interfere with the development of normal (protective) T cell immunity against aeroallergens and respiratory viruses, which are the principal agents of airway tissue damage in this group.

Particular attention has been given to the early use of inhaled steroids[26]. Initial findings have suggested that although steroids may provide symptomatic relief, there is as yet no definitive evidence of long-term disease modification[26]. More detailed follow-up studies are required in young children, in particular in the age range encompassing the 'initiation phase' (**Fig. 1a**). Animal studies have identified two issues of theoretical concern in relation to steroid use in early life, which need to be addressed in such studies. First, airway mucosal dendritic cells are central to the normal development of T_H1 immunity to respiratory viruses and to aeroallergens, and these cell populations are known to be highly susceptible to the effects of inhaled steroids. In particular, airway dendritic cell populations develop slowly during early life, and the rate of postnatal maturation of these important cellular networks can be retarded in animals with topical steroids[27]. Second, steroids have the potential to impair the growth of the developing lung; thus, it needs to be formally established that their use at early ages does not have long-term effects on lung function.

A range of alternative therapeutic approaches targeted at individual inflammatory effector molecules also seems feasible, in light of recent results with immunotherapy. In particular, therapies targeted at modulating T_H2 immunity seem logical candidates[28], given the weight of epidemiological evidence showing a close link between inhalant allergy and wheezing in children. Many other possibilities can also be considered, including passive and/or active immunization strategies aimed at limiting the degree of damage to growing airways by respiratory viral infections and the use of therapeutic agents to mimic the effects of natural exposure to environmental microbial stimuli[29,30], which have been shown to be protective against atopy and asthma in children[14]. Measures taken early to prevent[23] or reverse[22] allergic sensitization could provide an additional 'layer of protection' to the growing lung, potentially contributing to the permanent disappearance of wheezing (**Fig. 1c**).

Impediments to prevention

Despite the official recognition by bodies such as the US Food and Drug Administration and National Institutes of Health that children must be involved as subjects in the development and testing of new drugs[31], this position has not led to a change in the 'mindset' of the pharmaceutical industry. Testing of new drugs continues to follow an orderly progression from adults (18 years of age and older), to children 12 years of age and older and possibly to children 6–12 years of age. Apart from vaccines that are specifically designed for administration to children, few drugs are systematically tested below this age. A fundamental problem with the 'orderly progression' approach is that drugs that fail in adults are extremely unlikely to be tested in children, even if the rationale for their use is much stronger for children. The rumored deletion of several of the anti-T_H2 drugs from development pipelines represents a likely example. Although regulatory authorities have issued direct policy statements endorsing the importance of pediatric trials, they have not adopted an effective proactive stance, and until this occurs the status quo seems destined to be maintained. The emerging generation of asthmatics will be justified in asking why.

COMPETING INTERESTS STATEMENT
The authors declare that they have no competing financial interests.

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