

Therapeutic prospects for early asthma

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THE GLOBAL EPIDEMIC OF ASTHMA has triggered an international effort to understand the molecular basis of the disease and develop preventive or curative therapies. The pharmaceutical and biotechnology industries are investing billions of dollars in research to develop new classes of potential therapeutic agents. However, as our understanding of the molecular pathogenesis of asthma advances, the new insights gained into the disease may be best used to develop large-scale preventive interventions rather than new and expensive pharmaceuticals. We need to direct our efforts towards the most desirable therapeutic outcomes in early childhood, which include

- primary prevention of asthma;
- optimisation of lung function, especially in the first years of life;

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- suppression of disease exacerbations without impairing lung host defences;
- treatment of severe, refractory disease more safely and effectively;
- cure of established disease.

There is good evidence that immune deviation towards a net T_H2 cytokine pattern occurs early in asthma and contributes directly to disease (*see page S47*¹). However, in young children, mixed T_H1/T_H2 cytokine patterns have been found to be present concurrently. Physiologically, T_H1 - and T_H2 -biased immune responses reciprocally inhibit each other. It is a characteristic of lymphocyte immunobiology that during early immune deviation cytokine patterns remain plastic and can be realigned, but this plasticity is lost if stimulation is too intense or persists for too long.² In the early stages of asthma we perhaps have the best opportunity to use immune modulators to realign and fine-tune mucosal immunity away from an excessive T_H2 pattern and towards a neutral or balanced cytokine pattern. A fundamental ethical and medical issue is that almost all of the preventive agents currently envisaged would need to be given prophylactically to children at risk of asthma — yet our current

ABSTRACT

What we know

- There is strong evidence that T cells contribute to asthma pathogenesis.
- Immune-modulating drugs that dampen, turn off or redirect T cells, and adjuvants that trigger T_H1 immune responses, are potential therapies for preventing asthma.
- Current T cell immune suppressors are too toxic to use in very young children with asthma.
- Immune-modulation research is identifying pathways that might lead to preventive therapy for asthma.
- Inhibitors of T cell cytokines do not reduce asthma in adults.

What we need to know

- Is immune deviation from a T_H2-type response towards a T_H1-type response a sound strategy given that mixed T_H1/T_H2 responses are already known to occur in asthma?
- What, specifically, triggers the development of armed effector lymphocytes that are thought to cause tissue damage in asthma?
- Are the changes in lung structure that are observed in chronic asthma really dependent on T cell mechanisms?
- Can abnormal lung structure be improved or normalised?
- Would any of these strategies be safer and more effective than current therapies?

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understanding of the disease is such that we can not reliably or uniformly predict asthma risk in very young children.

In animals, a range of molecules able to trigger T_H1-type immune responses have been demonstrated to suppress T_H2-biased responses. As T_H1 responses can be highly damaging to the lung, any such intervention would need to be aimed at realigning immunity rather than converting it to a T_H1-biased pattern. It is a characteristic of these immune modulators that they invariably trigger a component of the ancient innate immune system. This system has evolved to rapidly distinguish highly conserved pathogen-associated-molecular-pattern molecules (PAMPs) (eg, gram-negative bacterial lipopolysaccharide [LPS]) to quickly prime specific immunity for the most appropriate cellular and humoral immune response. These agents (representing the IFN- γ /IL-12/IL-18 "T_H1 inducer" group) include recombinant human interferon IFN- α (rhIFN- α), rhIFN- γ , rhIL-12 and rhIL-18. To date, trials with these agents in adults have revealed a very narrow therapeutic window (between effect and toxicity) and produced trivial or no benefit. For example, a recent trial³ showed that IL-12, given in staggered and incremental doses, reduced sputum eosinophils and showed a weak trend towards improving histamine PC20, but had no effect on allergen-induced late responses. These minimal effects were produced at the cost of marked toxicity (arrhythmias, abnormal liver function, myalgia, and severe "flu"-like symptoms).

The observation that innate immune-response triggers often suppress T_H2-type responses has led to the development of a series of T_H1-inducing adjuvant-like molecules. These include derivatives of bacterial DNA CpG motifs, synthetic polymer T_H1 adjuvants, DNA vaccines, gene vectors, and several synthetic low molecular weight compounds (LMWCs). Advocates of this approach hope that insights gained from research into the "hygiene hypothesis" (which relates increased asthma risk to a decreased prevalence of infections that induce T_H1-biased immunity) may support the use of such agents in children at risk of asthma. It is not widely appreciated that steroids and beta-agonists both suppress T_H1 immunity, especially IL-12 production.^{4,5}

One particularly attractive area of research is the use of modified peptides derived from allergens as inhibitors of T cell function. The concept employed here is that introducing subtle changes into these peptides so that they still bind to major histocompatibility complex molecules, but imperfectly activate T cells, will result in T cell inactivation, thereby reducing asthma symptoms. This field has advanced considerably with the demonstration of "promiscuity" — the capacity of one peptide to bind to different MHC molecules, thus largely circumventing the problem of HLA variation in the general population. A logical extension of this work is to combine the peptide with a T_H1 adjuvant, as this could redirect the immune response if some residual T cell activation occurs.

A second, and conceptually less attractive, approach is to block key cytokines once disease has become established. Here, animal models predict inconsistent clinical outcomes, as several of the most promising potential blocking agents produce optimal outcomes only in very early disease and are ineffective against established disease. The agents of greatest current interest are blockers of the "T_H2" cytokines IL-4, IL-5, IL-9 and IL-13.⁶ A number of very advanced concepts for possible blocking mechanisms are now in late-stage development, including

- humanised or chimeric neutralising antibodies;
- muteins (genetically altered versions of the cytokine able to bind to the appropriate receptor but not trigger a response);
- antisense oligonucleotides and related derivatives (which are designed to neutralise the mRNA message for cytokines);
- rh-receptors (which serve as sequestering sinks for cytokines by binding them with high affinity in solution);
- LMWC inhibitors of key transcription factors critical for primary induction of IL-4-dependent T_H2 immune deviation;
- LMWC inhibitors of IL-13 effects targeted against the transcription factors STAT-6 and GATA-3.^{7,8}

A recent trial in adults of an anti-IL-5 antibody⁹ that strongly suppresses airway inflammation, especially eosinophilia, produced trivial benefits. It is arguable that this type of agent would be better used in children at an early stage of disease, before any structural change or longer-term deterioration in lung function has occurred (*see page S42*¹⁰).

Glossary

Antisense oligonucleotide	A synthetic version of RNA that binds to and inactivates the RNA message to produce a given protein.
Costimulation molecules	Molecules expressed on the surface of antigen-presenting cells together with an antigenic peptide that strengthen and fine-tune an immune response. T cells that do not "see" a costimulation signal are permanently inactivated. Examples include T1/ST2 and ICOS (inhibitory costimulation molecule).
Cytokines	Small proteins, released by various cell populations (eg, activated T cells), that regulate immune responses and inflammation.
DNA CpG motifs	Highly preserved DNA structures that are found in most bacterial DNA. CpG motifs trigger T _H 1-type responses.
GATA-3	A transcription factor found in T cells and associated with T _H 2 immunity.
HB-EGF, IGF, HGF/scatter factor, PDGF	Growth factors implicated in lung development, growth and also tissue remodelling in chronic inflammation.
Histamine PC20	The concentration of histamine that induces a reduction in FEV ₁ of 20%.
IFN-γ	Interferon gamma, a macrophage-activating cytokine.
IL-12	Interleukin 12, a cytokine strongly associated with induction of T _H 1 immune responses.
IL-18	Interleukin 18, a potent inducer of IFN-γ
IL-4 and IL-13	Interleukins 4 and 13, closely related cytokines that regulate T _H 2 immunity, IgE production and mucus release.
IL-5	Interleukin 5, a cytokine essential for eosinophil development.
IL-9	Interleukin 9, a cytokine implicated in asthma because of its association with inflammation, IgE production and mast cell growth.
LMWC	A low molecular weight compound (ie, a chemical drug substance).
LPS	Lipopolysaccharide (endotoxin), a component of gram-negative bacterial cell walls.
Mutein	An altered protein produced by genetic manipulation.
PAMPs	Pathogen-associated molecular patterns, a generic term for the signals intrinsic to diverse pathogens (such as LPS) that trigger innate immune responses.
PPARs	Peroxisome proliferator-activated receptors, a class of intracellular receptors implicated in lung differentiation, growth and inflammation.
Rh-receptors	Recombinant human receptors. These are modified human receptors, usually in soluble form, that act as decoys by binding to, and hence neutralising, molecules such as cytokines.
STAT-6	A transcription factor found in T cells and associated with T _H 2 immunity.
T_H1	A notional population of T helper cells, or a pattern of cytokines found in tissue, marked by a predominance of IFN-γ and little or no IL-4 and IL-5.
T_H2	A notional population of T helper cells, or a pattern of cytokines found in tissue, marked by a predominance of IL-4 and IL-5 and little or no IFN-γ.

It is very doubtful whether any of the broad immunosuppressors currently being developed (eg, third-generation cyclosporin derivatives and potent new T cell suppressors) would be appropriate for treating asthma in the first years of life, as their toxicity is too high. However, research into the fine specificity of T cell activation has revealed novel costimulation molecules that might prove very useful. Costimulation serves two roles that are mediated by distinct molecules: reinforcement and fine-tuning of T cell activation, and, through separate inhibitor molecules, termination or down-regulation of T cell activation (eg, via inhibitory costimulation molecule [ICOS]). As some important costimulation molecules (eg, T1/ST2) are preferentially expressed in T_H2-biased cell populations, it may be possible, by targeting these molecules, to achieve very selective immune manipulation in asthma.¹¹

Thus, although immune modulators offer potential promise in preventing and treating asthma, there are problems associated with their use. Apart from issues of intrinsic

safety, immune modulators seem to have little effect unless used in the early stages of disease, and memory/effector cells strongly resist immune deviation. Another, much more difficult, issue is that one of the most common serious problems in children with asthma is the occurrence of sudden exacerbations, which are most often triggered by infections, in which T_H2 immunity plays little or no role.

Children with small lungs at birth or incompletely developed alveolar septation caused by in-utero or early postpartum steroids are at increased risk of asthma. This has sparked an interest in lung-function-normalising agents for use in children. Such agents might include safe relatives of growth factors, such as retinoids (and synthetic thiazolidinediones or PPAR activators), and growth factors implicated in lung development, such as HB-EGF, IGF, HGF/scatter factor and perhaps the PDGF family. It is not yet known whether these agents can reverse steroid-induced lung underdevelopment.

A particularly important area of recent adult asthma research is persistence of abnormal lung function and structure despite steroid therapy. This has raised the issue of whether new drugs can block tissue matrix deposition, which, in model systems, governs the persistence and severity of asthma phenotype.

Despite the concerns raised here about the short- and long-term safety of immune modulators in early asthma, this is clearly the window in disease natural history where best outcomes might be achieved. It is also essential, to achieve true disease prevention, that we find better predictive markers of who might develop asthma.

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Drug delivery

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THE MAJORITY OF ISSUES regarding drug delivery in early childhood asthma concern inhaled drugs. Current aerosol delivery devices have changed little over the past 10 years. How good are they for use in young children, how can they be used optimally for this age group, and are they likely to survive another 10 years? The following questions address the most important issues relevant to delivery of inhaled drugs to young children.

How can pressurised metered-dose-inhaler-spacers be optimally used in children under five years of age?

Pressurised metered-dose inhalers (pMDIs) have been in common use for over 40 years and pMDIs combined with spacers (pMDI-Ss) have been used for over 20 years to assist in delivery to small children. Yet there have been few studies to determine optimal use of pMDI-Ss. There are a number of variables to consider.

Should a small or large spacer be used?

Small-volume spacers are recommended for use only in very young children.¹ However, the sole study investigating this

ABSTRACT

What we know

- In preschool children, small-volume spacers perform better than large-volume spacers.
- Detergent is the best antistatic agent for spacers, increasing lung delivery two- to threefold, but it must not be rinsed off.
- A mouthpiece should be used in children aged 2–3 years or older, as lung delivery is two- to threefold higher for oral inhalation than nasal inhalation (ie, by mask).
- Inhaled drug doses do not generally need to be reduced in infants and young children owing to inefficiencies of delivery in younger patients.
- Nebulisers are “dinosaurs” and not needed for most children with asthma.

What we need to know

- What is the best inhalation technique for spacers? How long should children breathe, how many breaths should they take, and at what age should they breath-hold?
- How should children, parents and doctors be instructed to achieve optimal levels of electrostatic charge reduction for spacers?
- How much should inhaled steroid dose be reduced when a spacer is used optimally?
- What dosing instructions should be given for β_2 -agonists delivered by spacer?

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