

Product Development

Breathless opportunities

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Senior Editor

Treatment of asthma has remained essentially unchanged for years and focuses on alleviating symptoms rather than disease modification. In large part, the state of the art reflects inertia on the part of the dominant big pharma players, who are focused on wringing out profits from respiratory drug franchises that topped \$15 billion in total sales in 2004. But advances also have been slowed by a lack of understanding of the causes of the disease and the fact that so many molecules appear to play a role in it.

Thus, the field today is where cancer was about a decade ago.

"Thinking in the past 30 years has been dominated by the leading two or three companies in the industry, but the existing treatments do little more than suppress the symptoms or inflammation, rather than modifying the outcome of the disease," said Stephen Holgate, Medical Research Council clinical professor of immunopharmacology at the University of Southampton in the U.K.

The existing paradigm for treating asthma is to give patients a combination of existing long-acting beta 2 agonist (LABA) bronchodilators and anti-inflammatory inhalable corticosteroids (ICS). While the vast majority of patients are well controlled with this regimen, the World Health Organization (WHO) estimates more than half the health costs of asthma are associated with the 5% of patients who have severe, persistent asthma that is poorly controlled.

In addition, an FDA warning issued last summer suggested that LABA containing therapies like Serevent salmeterol and the ICS/LABA combo Advair/Seretide may increase the chance of severe asthma episodes, as well as the chance of death when such episodes occur.

Holgate, who also is CEO and founder of Synairgen plc (LSE: SNG, Southampton, U.K.), believes that industry has been too complacent in its attitude toward asthma.

"There is still a misguided view that all we need is more inhaled steroids and long-acting beta 2 agonists. Yet the problem with these drugs is that patients have to continue taking them, often for life, since they either only suppress inflammation or relax smooth muscle without dealing with the underlying causes of the disease," he told BioCentury. "Clinicians want therapeutics that target the underlying causes of the disease."

In fact, potentially disease modifying approaches against new targets are in development at a number of biotech companies. The approaches include targeting a range of cells and molecules involved in this complex disease, among them IgE; a host of cytokines, chemokines and their receptors; prostaglandins; and kinases.

The first of the new therapies — Xolair omalizumab — is already on the market, and by the end of the decade more should be available or well on the way. In the meantime, a growing body

of research is pointing to a potential sea change in the approach to the disease, as genetic studies decouple the assumed links between asthma and allergy, offering new targets and therapeutic approaches.

'The concept that asthma is simply an extension of allergy to the lower airways is a gross oversimplification.'

— Stephen Holgate
of Synairgen

Complex disease

What makes asthma so difficult to treat is that several inflammatory cells are recruited and/or activated in the airways, releasing a variety of inflammatory mediators that have acute effects such as bronchoconstriction, plasma leakage and mucus secretion. These mediators ultimately also lead to tissue remodeling, including subepithelial fibrosis, increased vascularization and mucus-secreting cells, and thickening of airway smooth muscle.

The cells involved in the asthma process include lymphocytes, macrophages, eosinophils, mast cells and neutrophils, as well as airway epithelial and vascular endothelial cells. The

products of these cells include a multitude of interleukins, IgE and lipid mediators including prostaglandins and leukotrienes, which have emerged as potential asthma targets.

Further complicating the picture is the tangled nature of the interactions between these cells and molecules. For example, eosinophils are required for mucus accumulation, airway hyperresponsiveness (AHR) and airway remodeling.

A number of cytokines have been linked to eosinophil recruitment in airways, and some, such as interleukin-4, also are known to support differentiation of Th2 cells. Th2 cells orchestrate asthmatic inflammation through the secretion of a series of cytokines, including more IL-4, plus IL-13, IL-5 and IL-9. Th2 cells also stimulate IgE production. When IgE is cross-linked by an allergen presented by mast cells or basophils, histamine and other mediators of allergy are released.

Xolair targets IgE, which plays a central role in initiating and propagating the inflammatory cascade and thus the allergic response in affected tissues. Specific binding of free circulating IgE by the monoclonal antibody reduces both the early and the late allergic responses and symptoms of IgE-mediated allergy. As add-on therapy in severe asthma, Xolair reduces the requirement for inhaled corticosteroids and improves disease control.

Xolair was developed by Genentech Inc. (DNA, South San Francisco, Calif.); Tanox Inc. (TNOX, Houston, Texas); and

Novartis AG (NVS; SWX:NOVN, Basel, Switzerland). DNA reported \$320.6 million in U.S. sales in 2005. Xolair was approved in Europe in October 2005.

Cytokine soup

Cytokines play a critical role in orchestrating and perpetuating inflammation in asthmatic airways. There are several strategies for inhibiting pro-inflammatory cytokines in asthma, the most popular being the inhibition of secreted cytokines using blocking antibodies or soluble receptors.

So far, results have been mixed.

IL-4 and the related molecule IL-13 have emerged as the most popular cytokine targets. Both molecules signal through a shared receptor — IL-4 receptor alpha — and are known to promote IgE production and to be key mediators of the Th2 response.

MABs blocking IL-4 have been shown to inhibit allergen-induced AHR in animal models, and a soluble humanized IL-4 receptor has been shown to improve asthma control in patients with moderately severe asthma.

Before it was acquired by Amgen Inc. (AMGN, Thousand Oaks, Calif.) in 2002, Immunex Corp. had been working on an inhaled soluble humanized IL-4 receptor that prevented the decrease in lung function induced by ICS withdrawal in patients

Emerging asthma treatments

Of at least 28 novel asthma products in clinical development, 26 are in Phase I or II trials, suggesting a wave of therapeutics against new targets is about to enter mid- to late-stage development. The list excludes products based on already established mechanisms such as leukotriene modifiers, corticosteroids, anti-cholinergics and adrenergic bronchodilators, which are mainly being pursued by big pharma. In fact, big pharma has disclosed ties to only seven compounds aimed at new targets. (A) Under a 2005 deal, Discovery Labs (DSCO) will use Chrysalis' technology to deliver the aerosolized formulation of the compound; (B) Hydroxychloroquine is already approved for malaria, systemic lupus erythematosus and rheumatoid arthritis; NA = Not applicable

Company	Product	Description	Target	Status
Genentech/Tanox/ Novartis	Xolair omalizumab	Humanized MAb against IgE	IgE	Mkt (adults/ adolescents); Ph III (pediatric)
Altana	Daxas roflumilast	Phosphodiesterase-4 (PDE-4) inhibitor	PDE-4	Ph III; MAA withdrawn in Nov 05
Avontec	AVT-01	Decoy oligonucleotide directed against an undisclosed pro-inflammatory transcription factor	Undisclosed transcription factor	Ph II
Celgene	CC-10004	PDE-4 inhibitor	PDE-4	Ph II
deCode	MAP3K9 inhibitor	MAP3K9 kinase inhibitor	MAP3K9 kinase	Ph II
GlaxoSmithKline	Mepolizumab	Humanized MAb against interleukin-5 (IL-5)	IL-5	Ph II
GlaxoSmithKline	274150	Selective inducible nitric oxide synthase (iNOS) inhibitor	Nitric oxide synthase	Ph II
Inflazyme	IPL512,602	Oral 2nd-generation leukocyte selective anti-inflammatory drug (LSAID)	Unknown	Ph II
MediciNova/Kyorin	MN-001	Leukotriene receptor antagonist and an inhibitor of PDE-4, 5-lipoxygenase and thromboxane A2 (TXA2)	PDE-4, 5-lipoxygenase, TXA2	Ph II
PDL BioPharma/ Roche	Daclizumab	Humanized MAb against CD25	IL-2 receptor alpha chain (CD25)	Ph II
Revotar/Encysive	Bimosiamose	E-, P-, and L-selectin antagonist	Selectin	Ph II
Roche	R411	Small molecule dual integrin antagonist	Integrin	Ph II

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with moderately severe asthma. But that compound, Nuvance, failed to show benefit versus placebo in Phase II trials in patients with milder asthma.

PDL BioPharma Inc. (PDLI, Fremont, Calif.) also took a shot at IL-4. Its SB240683, in-licensed from Glaxo-SmithKline plc (LSE:GSK; GSK, London, U.K.) in 1999, was a humanized MAb against IL-4 to treat steroid-naïve patients with mild to moderate asthma. The program was halted after failing to show benefit in a Phase IIa trial.

PDLI has since turned its attention to IL-2. "We are developing daclizumab to treat moderate to severe persistent asthma that is not well controlled despite the use of inhaled corticosteroids," said spokesperson James Goff. "If approved, we believe daclizumab would be appropriate for a potentially larger group of patients than the only biologic currently on the market, which is limited to allergic asthmatics."

PDLI plans to begin a Phase IIb study in the second half.

Daclizumab, which targets the IL-2 receptor alpha chain (CD25), has been marketed since 1997 as Zenapax by Roche (SWX:ROCZ, Basel, Switzerland) to prevent acute kidney transplant rejection.

After reporting positive Phase II data in the spring of 2004, PDLI signed a deal with ROCZ that yielded \$17.5 million up front plus the potential for up to \$187.5 million in milestones for rights to co-develop and co-commercialize daclizumab in the U.S. for asthma and related respiratory diseases. PDLI will receive royalties on asthma sales outside the U.S.

Probably the most important interleukin target is IL-13, which has been linked to AHR, mucus hypersecretion and airway fibrosis, independent of eosinophilic inflammation. IL-13 is thought to induce steroid resistance, possibly by activating p38 mitogen-activated protein

(MAP) kinase. IL-13 signals through IL-4 receptor alpha, IL-13 receptor alpha 1 and IL-13 receptor alpha 2.

Cambridge Antibody Technology Group plc (LSE:CAT; CATG, Cambridge, U.K.) is developing a humanized anti-IL-13 MAb for severe asthma. Last year, the company completed a Phase I trial of CAT-354 in 34 patients and had intended to start a Phase I/II clinical pharmacology trial in the fourth quarter of 2005. An update was expected this week with CAT's first quarter earnings announcement.

An elegant approach being entertained by several companies is to develop compounds that target IL-4 and IL-13 simultaneously. Most advanced with clinical candidates are Aerovance Inc. (Berkeley, Calif.); AMGN; and Regeneron Pharmaceuticals Inc. (REGN, Tarrytown, N.Y.).

REGN's IL-4/13 Trap is a fusion of two distinct receptor components and an antibody Fc region that captures or traps the

Emerging Asthma Treatments, from previous page

Company	Product	Description	Target	Status
AirPharma/Britannia	Zofac (AP0016)	Inhaled dry powder formulation of Britannia's Pumactant synthetic surfactant	NA	Ph II
Topigen	ASM8	Dual modified phosphorothioate antisense oligonucleotides (AS-ODNs) that inhibit multiple inflammatory pathways	Unknown	Ph II
Dynavax	ISS-1018	Immunostimulatory DNA sequences (ISS)	Toll-like receptor 9 (TLR9)	Ph IIa
Discovery Labs/ Chrysalis (A)	DSC-104	Inhaled aerosol formulation of humanized lung surfactant	NA	Ph I compl
Amgen	AMG 317	MAb against IL-4 and IL-13	IL-4/IL-13	Ph I
AstraZeneca	AZD3778	Chemokine receptor antagonist	Chemokine receptor	Ph I
Avanir	AVP 13358	Oral inhibitor of IgE antibody, CD23 and Th2 cytokine production	IgE, CD23	Ph Ib
Cambridge Antibody CV Therapeutics	CAT-354 CVT-6883	Human MAb against IL-13 Adenosine A2B receptor antagonist	IL-13 Adenosine A2B receptor	Ph I Ph I
GlaxoSmithKline	256066	Inhaled PDE-4 inhibitor	PDE-4	Ph I
Glenmark/Forest	Oglemilast	Long acting PDE-4 inhibitor	PDE-4	Ph I; start Ph II in 06
LAB International	LAB CGRP	Inhaled calcitonin gene-related peptide	Calcitonin gene-related peptide receptors	Ph I
MedImmune/Genaera	IL-9 inhibitor	MAb targeting IL-9	IL-9	Ph I
Regeneron	IL-4/13 Trap	Recombinant protein containing the extracellular domains of the IL-4 and IL-13 receptors linked to the Fc portion of human IgG	IL-4/IL-13	Ph I compl
Synairgen	Interferon beta	Inhaled interferon (IFN) beta	IFN receptor	Ph I for cold virus-induced asthma attacks
UCB	CDP323	Small molecule inhibitor of alpha-4 integrins	Integrin alpha (4)	Ph I

targeted cytokines. This molecule is designed to bind both IL-4 and IL-13, preventing their interaction with cell surface receptors. IL-4/13 Trap has completed a Phase I trial in mild to moderate asthma

Aerovance, which was spun out of Bayer AG in 2004, has Aerovant (AER-001), a recombinant human IL-4 that binds to and blocks both the IL-4 receptor and IL-13 receptor alpha I. It is thought to work by inhibiting the assembly of the IL-4 and IL-13 receptor complexes. Originally in-licensed from Bayer (FSE:BAYG; BAY, Leverkusen, Germany), which called it BAY 36-1677, Aerovant is in Phase I/II trials.

AMGN's AMG 317, a MAb targeting the two receptors, also is in Phase I.

Zenith Therapeutics Ltd. (ASX:ZTL, Richmond, Australia) and partner Merck & Co. Inc. (MRK, Whitehouse Station, N.J.) are developing MAbs that target IL-13 receptor alpha I to inhibit IL-13 activity. In August 2005, the partners selected an optimized lead for preclinical development. MRK is responsible for all clinical development and marketing.

Domantis Ltd. (Cambridge, U.K.) is taking a slightly different tack, focusing on the cytokines rather than their respective receptors. "It is Domantis' contention that IL-4 and IL-13 are part of a redundant pathway, and to have a meaningful effect on disease, you need to simultaneously inhibit IL-4 and IL-13. Inhibiting one or the other will provide only a partial response or no response at all," EVP and CSO Ian Tomlinson told BioCentury.

Domantis' technology is focused on human domain antibodies (dAbs) that are made of the smallest functional binding units of human antibodies, corresponding to the variable regions of either the heavy or light chains. Domantis' approach in asthma is to link a pair of dAbs in a single product, each of which binds to one of the cytokines.

Because the molecules are small and stable, Tomlinson said, Domantis believes they will be amenable to delivery via a range of dry powder and liquid-based pulmonary formulations. The

company is finalizing a drug candidate and is looking for commercial partners with expertise in asthma to take it into clinical development.

"It is clear that many pharmaceutical companies that have traditionally been small molecule players are now looking for biologics to extend their franchises in these areas," Tomlinson said. "Because biologics are likely to provide a very different clinical outcome to the existing small molecules, they could fulfill two quite separate roles: either for use in combination with them, or as replacements for them."

Still more cytokines

Beyond IL-4 and IL-13, other cytokines that have attracted attention as potential asthma targets include IL-5, IL-9 and several chemokines.

Blocking IL-5 inhibits eosinophilic inflammation and AHR in primate models of asthma. The first effort in the clinic failed: GlaxoSmithKline's mepolizumab, a humanized MAb against IL-5, reduced circulating eosinophils by more than 95% in Phase II trials but provided no significant improvement in either asthma symptoms or lung function. The product is being developed as an anti-inflammatory to treat hypereosinophilic syndrome.

BioWa Inc. (Princeton, N.J.), a subsidiary of the Japanese pharma company Kyowa Hakko Kogyo Ltd. (Tokyo:4151, Tokyo, Japan), believes the target remains worth pursuing. It has an anti-IL-5 receptor in late preclinical development. BioWa has exclusive worldwide rights except in Asia, where Kyowa retains rights.

Another potential target is IL-9. Expression of both the cytokine and its receptors is increased in asthmatic airways in mouse models. IL-9 is linked to Th2-driven inflammation, amplification of mast cell mediator release and IgE production, as well as mucus hypersecretion.

MedImmune Inc. (MEDI, Gaithersburg, Md.) is evaluating the potential of MAbs targeting IL-9 to treat or prevent symptomatic, moderate to severe, persistent asthma. Early last year, MEDI

Promising targets for asthma

Given the complexity of the condition, many different approaches can be taken to tackle asthma. A better understanding of the underlying pathobiology and genetics of the condition has opened the door to new possibilities.

Therapeutic approach

Mode of action

Anti-IgE	<ul style="list-style-type: none"> Release of mediators from mast cells is IgE-dependent, and blocking its activation has been shown to be effective. Can be achieved by targeting either high affinity IgE receptor (omalizumab) or the low affinity IgE receptor (anti-CD23)
Anti-interleukins	<ul style="list-style-type: none"> Anti-interleukins block key inflammatory responses such as eosinophil recruitment and subsequent airway hyperresponsiveness by targeting IL-5 and IL-9, and by blocking IgE production in case of IL-4 and IL-13
Blocking chemokine receptors	<ul style="list-style-type: none"> Several chemokines, such as eotaxins and monocyte chemoattractant protein-4 (MCP4), are involved in the pathophysiology of asthma by activating chemokine receptors. Antagonists to the three most significant receptors — CCR3, CCR2 and CCR4 — are in development.
Blocking signal transduction pathways	<ul style="list-style-type: none"> A number of kinases have been implicated in inflammation. Favorite targets are the p38 mitogen-activated protein (MAP) kinase, involved in the synthesis of many important inflammatory proteins relevant to asthma, and Syk kinase, which is involved in signaling the high affinity IgE receptor in mast cells.
Inhibiting phosphodiesterases	<ul style="list-style-type: none"> Phosphodiesterase-4 (PDE-4) inhibitors have shown broad anti-inflammatory activity, including inhibition of eosinophil recruitment and blocking activation of key inflammatory cells such as mast cells and eosinophils. Most advanced compounds have reached Phase III, but side effects have held them back.
Blocking cell adhesion	<ul style="list-style-type: none"> Migration of inflammatory cells into tissues is mediated by glycoprotein molecules, such as integrins and selectins, on both inflammatory cells and structural cells such as epithelial cells. Inhibition of these molecules might prevent such infiltration.

completed a Phase I study in healthy adults with its lead anti-IL-9 MAb in collaboration with Genaera Corp. (GENR, Plymouth Meeting, Penn.), which has been researching the role of IL-9 and its receptor in the pathogenesis of asthma and other respiratory disorders.

Meanwhile, more than 50 different chemokines have been linked to the recruitment of inflammatory cells through activation of chemokine G protein-coupled receptors (GPCRs), which are very amenable to small molecule inhibition. Three of these have emerged as asthma targets — CC chemokine receptor 2 (CCR2), CCR3 and CCR4 — although they are not exclusively associated with the condition, as antagonists are being developed to treat other inflammatory conditions.

Most advanced are efforts to develop small molecule inhibitors of CCR3, which has a role in recruiting eosinophils and mast cells to the lung. GlaxoSmithKline (LSE:GSK, GSK, London, U.K.) has a compound in Phase II trials, while other companies are still exploring research opportunities.

Antigen Express Inc., a subsidiary of Genex Biotechnology Corp. (GNBT, Toronto, Ontario), is taking a different tack based on the fact that Th1- and Th2-related cytokines generally act antagonistically. Antigen believes Th1 stimulation is ideal for the immunotherapy of allergy.

The company's immunotherapy approach to asthma and allergic rhinitis is based on a peptide vaccine containing MHC class II antigenic epitopes of allergens. These peptides are hybrids linking the li-protein's immunoregulatory segment, called the li-Key peptide, to an MHC class II epitope peptide of an allergen. Such MHC complexes are known to be potent stimulators of very strong Th1 responses in mice and in human lymphocyte cultures.

"By switching the allergen response from Th2, which promotes IgE, to Th1, which also suppresses the allergic response by additional mechanisms, good clinical benefits can be achieved," Antigen CSO Bob Humphreys said. The company is collaborating with Stallergenes S.A (Antony, France) to design and test li-Key/allergen epitope hybrid peptides. They have molecules in research.

Agonists of toll-like receptor 9 (TLR-9) also up-regulate Th1 while suppressing Th2 responses. Dynavax Technologies Corp. (DVAX, Berkeley, Calif.); Coley Pharmaceuticals Group (COLY, Wellesley, Mass.); and Idera Pharmaceuticals Inc. (IDP, formerly

Hybridon Inc., Cambridge, Mass.) are developing TLR-9 agonists for the indication.

Prostaglandin antagonism

Another angle is to focus on prostaglandins, some of which play a role in inflammation.

In mice, deletion of prostaglandin D2 receptors has been shown to inhibit inflammatory responses to allergens, and AHR. Prostaglandin D2's role is to activate the chemoattractant receptor of Th2 cells, prostaglandin D2 receptor.

PGD2, more commonly known as chemoattractant receptor homolog CRTH2, is a GPCR that is selectively expressed on Th2 cells, eosinophils and basophils, but not Th1 cells. It has been suggested that CRTH2 is involved in cell activation and chemotaxis and occupies a pivotal role in the development of Th2 responses.

Sosei Co. Ltd. (Tokyo:4565, Tokyo, Japan), in collaboration with Abgenix Inc. (ABGX, Fremont, Calif.), has identified two human MABs against CRTH2. ABGX and Sosei have planned to co-develop the antibodies, although it is not clear what will happen to the collaboration now that AMGN is acquiring ABGX.

Microbia Inc. (Cambridge, Mass.) also is working on an oral, once-daily treatment targeting CRTH2. According to CEO Peter Hecht, the company has identified a highly potent, nanomolar-level CRTH2 antagonist that showed "excellent oral bioavailability and potency." Microbia hopes to begin Phase I trials in 2007.

7TM Pharma A/S (Copenhagen, Denmark) also is believed to have a CRTH2 antagonist in late lead optimization. Although it has never identified the target, last year 7TM entered into an exclusive worldwide license with Ortho-McNeil Pharmaceutical, a unit of Johnson & Johnson (JNJ, New Brunswick, N.J.), to develop oral antagonists against a GPCR that is associated with asthma and allergic diseases.

Another company believed to be working on the target is Oxagen Ltd. (Abingdon, U.K.). "We are shooting for a once-a-day oral anti-inflammatory medicine," said CEO Mark Payton. "It is our intention to out-license a compound following clear demonstration of efficacy in patients."

The company's work has attracted a lot of interest from

Asthma vs. COPD

At first glance, asthma and chronic obstructive pulmonary disease look very similar in that both are chronic inflammatory diseases involving bronchoconstriction and mucus production. Both also have strong gene/environment interactions. However, there are stark differences. Inflammation associated with asthma is primarily eosinophilic with the predominant involvement of mast cells and CD4+ T lymphocytes, while COPD is characterized by neutrophilic inflammation mediated by macrophages and CD8+ T lymphocytes. Not surprisingly, this has an impact on how patients respond to treatment. Additional differences are noted below. *Source: Spiriva.com*

Factors	Asthma	COPD
Age when it starts	<ul style="list-style-type: none"> •Typically in childhood •Does not generally worsen with age 	<ul style="list-style-type: none"> •Later in adulthood, but as soon as the early 40s •Worsens with age
Triggers/Causes	<ul style="list-style-type: none"> •Allergens (dust, plants, animals, etc.) •Weather •Heredity 	<ul style="list-style-type: none"> •Directly linked to smoking •Less commonly triggered by inhaled fumes, pollution, dust and chemicals
Symptoms	<ul style="list-style-type: none"> •Patient often symptom-free between attacks 	<ul style="list-style-type: none"> •Chronic
Airflow	<ul style="list-style-type: none"> •Usually, treatment can quickly and fully restore airflow 	<ul style="list-style-type: none"> •Some airflow can be restored by quitting smoking and taking prescribed medicines

investors, including MPM, which led a \$60 million venture round last year to underpin the development of the lead anti-inflammatory compound.

Kinases

Protein kinases, which are important to the production of a number of key inflammatory proteins, are widely considered to be among the hottest emerging targets for asthma.

Among the most interesting compounds are inhibitors homing in on the p38 MAP kinase pathway, which is at the heart of expression of a number of inflammatory proteins associated with asthma. There is also evidence that p38 MAP kinases may have a role in corticosteroid resistance in asthma patients.

A number of cytokine suppressant anti-inflammatory drugs (CSAIDs) have been looked at as p38 MAP kinase inhibitors, although they have been more linked to chronic obstructive pulmonary disease (COPD). Their potential broad spectrum anti-inflammatory activity also suggests the possibility for side effects.

Steroid resistance in asthma also has been associated with increased activation of another kinase — c-jun N-terminal kinase — which suggests inhibition of JNKs might be useful for severe asthmatics who are not responding to steroids. Researchers at Celgene Corp. (CELG, Warren, N.J.) were able to demonstrate in a mouse model of allergic asthma that JNK inhibition reduced allergen-induced increases in eosinophils and lymphocytes, while another JNK inhibitor reduced proliferation of airway smooth muscle cells in mice after allergen exposure.

Another kinase considered a potential hot target is Syk, a protein tyrosine kinase that regulates IgE receptor signaling in mast cells. Unlike common allergy and asthma drugs that block only a single chemical mediator, Syk inhibitors block the major IgE dependent pathways in mast cells that trigger an allergic attack, potentially making these inhibitors more effective and comprehensive drugs.

Rigel Pharmaceuticals Inc. (RIGL, South San Francisco, Calif.) and partner Pfizer Inc. (PFE, New York, N.Y.) are developing small molecule Syk kinase inhibitors to treat allergic asthma and COPD). The compounds are in preclinical development and will be delivered using a dry powder inhaler.

Unfulfilled promise

While phosphodiesterases have been shown to inhibit the recruitment and activation of key inflammatory cells and the hyperplasia and hypertrophy of structural cells, results from human trials have been disappointing.

PDE-4, the predominant PDE enzyme in inflammatory cells, catalyzes the hydrolysis of cyclic AMP to AMP, and as such has a key role in maintaining cAMP levels, which in turn have a critical role in signal transduction, down-regulating activation of intracellular processes. PDE-4 is expressed in almost all key inflammatory cells involved in asthma and COPD.

Established asthma drugs		
Established treatments for asthma.		
Anti-allergy		
Drug class	Mode of Action	Key examples
Antihistamines	Block action of histamine	Mostly generics such as loratadine
Mast cell stabilizers	Prevent release of histamine (and other allergic reaction chemicals) at mast cells	Cromoglicate
Anti-IgE	Block IgE	Omalizumab
Anti-inflammatories		
Corticosteroids	Decrease inflammatory response in airways	Fluticasone
Bronchodilators		
Anti-cholinergics (muscarinic receptor antagonists)	Block action of acetylcholine to prevent contraction of the bronchial smooth muscles	Ipratopium bromide
Beta 2 agonists	Relax muscles in airways to enhance airflow	Salbutamol, Salmeterol, Formoterol
Leukotriene receptor antagonists	Block leukotriene action	Zafirlukast
Xanthines	Relax muscles in airways	Theophylline

Indeed, evidence of its overexpression in atopic patients prompted the belief that it might be a target as an anti-inflammatory treatment in asthma. But PDE-4 inhibitors have a mixed record. Altana Pharma AG (FSE:ALT; AAA, Konstanz, Germany) withdrew its MAA for Daxas roflumilast to treat asthma and COPD after discussions with the EMEA. The company plans to submit a new MAA after additional data are available.

Vomiting and nausea are side effects associated with PDE-4 inhibitors, including theophylline, a nonselective PDE-4 inhibitor that has long been used as an add-on asthma treatment. Some believe the side effects may be associated with the PDE-4D subtype, and that developing subtype-selective PDE inhibitors, against PDE-4B in particular, could be beneficial.

Unlinking allergy, asthma

While most of the new approaches are based on the molecules that are up-regulated in both allergy and asthma, the newest thinking suggests that asthma may be caused by disordered epithelial function.

“The concept that asthma is simply an extension of allergy to the lower airways is a gross oversimplification,” according to Holgate. “What we should be doing is developing new treatments that improve epithelial function to protect the airways from multiple environmental insults known to be linked to asthma, such as air pollution, virus infection and allergens.”

However, one of the major challenges is the absence of good predictive animal models. Indeed, according to Holgate, the allergy-based view of asthma affects preclinical testing and ultimately the choice of compounds

“However,” he said, “epidemiology shows no relationship between allergen exposure and new asthma. Instead, epidemiology is pointing to infection, pollutants, diet and obesity as risk

factors for the origins of asthma.”

Thus, a number of critical events identified in animal models have not translated to human disease. Particularly discouraging has been the lack of success with approaches targeting IL-4 and IL-5.

Holgate blames this on the models rather than the targets.

“At Synairgen we have developed in vitro human disease-based tissue and cell models that reproduce the disease phenotypes to allow us to discover new molecular targets relevant to the human disease and enabling us to also test novel therapeutic entities,” he said. “This is how we discovered beta interferon as a novel therapeutic target for virus-induced exacerbations of asthma and COPD.”

According to Holgate, the company’s models of human disease have shown that asthmatic airways produce little or no interferon beta, which acts as a defense against the virus’ ability to replicate. “This has led us to develop an inhaled interferon beta program, and we hope to demonstrate the utility of this approach in a proof-of-concept study of therapeutic efficacy.”

Last November, SNG began a U.K. Phase I study in 27 healthy volunteers.

SNG, in collaboration with the School of Medicine at the University of Southampton, intends to phenotype human tissue samples from asthmatic and healthy subjects to identify genetic differences.

“Almost all the new genes that have been discovered as susceptibility genes in asthma are expressed in the epithelium or underlying mesenchymal cells,” said Hogate.

A number of asthma genes or gene complexes have now been identified. DPP10, GPRA and SPINK5 are found in the outer layer of airway epithelium cells and are thought to have some role in epithelial defense.

DPP10 (dipeptidyl peptidase 10 gene) encodes a peptidase that is thought to attack cytokines. GPRA encodes a GPCR that is up-regulated in epithelial cells in inflamed airways. SPINK5 encodes a multidomain serine protease inhibitor that is thought to be active against multiple substrates.

ADAM33, the first asthma susceptibility gene to be identified through positional cloning, is expressed in bronchial smooth muscle cells and is thought to influence bronchial hyperresponsiveness. It is likely to be linked to myogenesis, as it is found in other muscles.

PHF11, the second positionally cloned gene for asthma, appears primarily to influence total IgE levels.

Exposure to microbes in childhood is thought to protect against asthma. This is mediated by a number of microbial

pattern-recognition receptors such as CD14, toll-like receptor 2 (TLR2), and TIM-1, which are expressed on dendritic and epithelial cells among others. Polymorphisms in CD14, TLR2 and TIM-1 have all been shown to influence asthma susceptibility.

While positional cloning is proving to be a powerful tool for homing in on asthma susceptibility genes and pathways not before linked to asthma pathogenesis, it will take some time for these insights to translate into realistic therapeutic options.

In the meantime

Despite all the new targets being worked on by biotechs, the major players in the respiratory markets are focused in the short term on creating improved combinations from their existing arsenals.

Three companies account for the vast bulk of sales in asthma, with GSK the undisputed leader. Indeed, Advair/Seretide, a combination of the LABA Serevent salmeterol and the ICS Flixotide fluticasone in a single inhaler, is the company’s best selling drug, posting 2004 sales of £2.5 billion (\$4.5 billion).

At MRK, almost all respiratory drug sales of \$2.6 billion in 2004 came from Singulair montelukast, which is approved both for chronic asthma and seasonal allergic rhinitis.

Meanwhile, AstraZeneca plc (LSE:AZN; AZN, London, U.K.) recorded \$1.1 billion in 2004 sales of its ICS product, Pulmicort budesonide, and \$797 million for its

Symbicort budesonide/formoterol ICS/LABA combination.

The stand-out deal in the “me-better” race is the 2003 alliance between Theravance Inc. and GSK, which is focused on pooling their respective LABA compounds. In addition to an initial \$50 million payment from GSK, THRX (San Francisco, Calif.) is eligible for milestones of up to \$495 million, and double-digit royalties on any sales from the pool, regardless of the compound’s origin.

The deal should help GSK ward off the likely sales slump following the expiry of Advair patents in 2010. The lead compound in the so-called Beyond Advair collaboration, GSK159797, showed clinically significant increases in bronchodilation over 24 hours with little impact on heart rate in a Phase II study.

The “me-better” bandwagon is reinforced by speculation that NVS may link up with Schering-Plough Corp. (SGP, Kenilworth, N.J.) to develop a once-daily ICS/LABA combination based on SGP’s ICS mometasone and the Swiss pharma’s indacaterol (QAB149) LABA.

‘It is clear that many pharmaceutical companies that have traditionally been small molecule players are now looking for biologics to extend their franchises in these areas.’

— Ian Tomlinson of Domantis

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