Toll gate against allergic asthma

By Tim Fulmer, Senior Writer

Marketed treatments for allergic asthma, including corticosteroids and adrenergic receptor β_2 agonists, have focused on intervening downstream from the initial inhalation of an allergen. Now, a team of Belgian and American researchers has proposed treating allergic asthma by antagonizing toll-like receptor 4 on cells that line the airway and have direct contact with airborne allergens.¹

The group thinks that the ability to decrease multiple proinflammatory factors in the allergic asthma cascade could give the compounds an advantage over other asthma therapeutics and is looking for industry partners to take the approach into the clinic.

Previous work has shown that, in addition to serving as a physical barrier, airway epithelial cells sense the presence of airborne allergens via toll-like receptor 4 (TLR4). The epithelial cells then activate dendritic cells (DCs) and potentially contribute to downstream inflammation and allergic asthma²⁻⁴ (see **Figure 1**, "Allergens take their toll on asthma").

Bart Lambrecht and colleagues decided to test whether inhibiting TLR4 on airway epithelial cells was sufficient to decrease or prevent bronchial hyper-reactivity associated with allergic asthma. Lambrecht is professor of immunology and respiratory medicine at Ghent

University and professor of pulmonary medicine at the Erasmus University Medical Center.

As reported in *Nature Medicine*, the team used mice with TLR4-deficient airway epithelial cells. In these mice, exposure to

Figure 1. Allergens take their toll on asthma. Research published in *Nature Medicine* suggests that blocking interactions between toll-like receptor 4 (TLR4) and allergens on airway epithelial cells could help treat allergic asthma.

[a] Airborne allergens bind TLR4 expressed on the surface of airway epithelial cells, triggering the release of multiple cytokines and chemokines including monocyte chemoattractant protein-1 (CCL2; MCP-1) and chemokine C-C motif ligand 20 (CCL20; MIP3A).

[b] Increased levels of chemokines attract and activate airway dendritic cells (DCs), which subsequently activate T helper cells.

[c] Activated T helper cells secrete multiple proinflammatory cytokines, including IL-4 and IL-13, which activate antibody-producing B cells.

[d] High levels of the resulting IgE antibodies induce degranulation of mast cells and histamine release, leading to the classic symptoms of allergic asthma.

A number of strategies are in development or marketed to intervene at various points in the allergic cascade to decrease or prevent symptoms associated with allergic asthma.

lipopolysaccharide (LPS) in the trachea resulted in lower influx of proinflammatory neutrophils, monocytes and DCs into lung tissue compared with that seen in wild-type mice. Importantly, mucosal DCs from the TLR4-deficient mice had a lower ability to drive the proliferation and differentiation of T cells, which are central players in allergic asthma.

Next, the researchers administered house dust mite extracts to the TLR4-deficient mice. The extracts were a complex mixture of multiple allergens and also contained LPS. The TLR4-deficient mice had fewer monocytes and DCs in airway tissue and lower levels of proinflammatory cytokines and chemokines in the bronchoalveolar lavage than wild-type controls.

Finally, in wild-type mice exposed to house dust mite extract, intrapulmonary delivery of a TLR4 antagonist in combination with extract challenge led to less airway inflammation and hyper-reactivity than that seen in wild-type mice that received vehicle control in combination with extract challenge.

Lambrecht, the corresponding author, told *SciBX* that targeting TLR4 on airway epithelial cells could have advantages over targeting individual cytokines to treat asthma.

“By antagonizing TLR4 on airway epithelial cells, our strategy targets a receptor that sits most upstream in the allergy cascade. Blocking the initial interaction of TLR4 with an airborne allergen should thus prevent or at least reduce activation of multiple downstream proinflammatory cytokines that play a role in allergic asthma. This could offer a real advantage over compounds that target a single downstream cytokine to treat disease,” he said.

All about allergens

Lambrecht said he is in talks with potential industry partners that have TLR4 antagonists. He added that he wants to design and help run a small proof-of-concept trial in allergic asthma patients.

Disclosed TLR4 antagonist programs include NI-0101, a humanized mAb that antagonizes TLR4 from **NovImmune S.A.** The compound is in preclinical testing to treat autoimmune and inflammatory diseases.

At least three companies have small molecule TLR4 antagonists. **GlaxoSmithKline plc** gained CRX-526 when it acquired Corixa Corp. in 2005. **Eisai Co. Ltd.**’s Eritoran (E5564) is in Phase III testing to treat severe sepsis. Earlier this year, **Takeda Pharmaceutical Co. Ltd.** discontinued a Phase III trial of TAK-242 to treat sepsis. The company did not give a reason for the decision.

Asthma researcher Christopher Karp wanted to see additional proof of concept in preclinical allergy models. Karp is director of the Division of Molecular Immunology and professor of pediatrics at the

Cincinnati Children’s Hospital Medical Center and the **University of Cincinnati College of Medicine**.

“The *Nature Medicine* paper does an excellent job illustrating the critical role that TLR4 on airway epithelial cells plays in driving allergic response to the house dust mite allergen extracts,” he said. “An interesting therapeutic question is how central TLR4 is to the recognition of many other common allergens. The researchers might now try antagonizing TLR4 in preclinical allergy models driven by other allergens—such as from *Aspergillus* mold or the cockroach—to see if they get similar results.”

Lambrecht said his lab is indeed looking at TLR4 antagonism in additional preclinical models, although for now they are focusing on dust mite allergen.

“We plan to look at the TLR4 antagonists in a humanized murine model of asthma driven by dust mite allergen,” Lambrecht told *SciBX*. “These mice are reconstituted with peripheral blood mononuclear cells from house dust mite allergy patients, and efficacy in these animals should lend further support to using TLR4 antagonists in patients.”

Karp also wanted to see the TLR4 antagonist delivered after allergen challenge and the establishment of asthma, rather than together with challenge. He said that could give insight into the potential importance of timing of treatment.

Earlier this year, Karp and colleagues published data that showed a single allergen, Der p 2, isolated from a house dust mite allergen extract elicited allergic asthma in murine models in a TLR4-dependent manner.⁵

Lambrecht told *SciBX* the *Nature Medicine* findings have not been patented.

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