Atopix Therapeutics Ltd.

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Late-stage atopic dermatitis treatment on target

With OC459, a first-in-class, oral, once-a-day small molecule for atopic dermatitis, Atopix has a potential winner for this and other type 2 helper T cell–mediated disorders such as severe asthma and related allergic conditions.

Clinical-stage biotech Atopix, a leader in the development of novel treatments for type 2 helper T (T_H2) cell–mediated disorders, has accrued a pipeline of oral, once-a-day small-molecule prostaglandin D_2 receptor 2 (CRTH2) antagonists with the potential to offer advanced therapeutic solutions for conditions such as atopic dermatitis and severe asthma.

Traditionally, the treatment of severe atopic dermatitis has included the systemic use of steroids or calcineurin inhibitors (cyclosporines), but the elevated risk of widespread immunosuppression and other unwanted effects associated with these treatment options has driven the search for alternative therapeutic strategies.

One mechanism in particular—prostaglandin D_2–mediated CRTH2 activation on T_H2 cells—has garnered interest over the past decade owing to its exquisite specificity for the T_H2 arm of the immune system, which prevents immunosuppressive side effects. However, several efforts to harness this pathway for therapeutic intervention were unsuccessful because of pharmacological and study-design shortcomings, particularly the failure to target the appropriate patient populations.

Atopix's lead compound, OC459, is highly specific and potent while exhibiting excellent drug-like characteristics. Clinical development of the compound focused on particular patient groups categorized on the basis of disease mechanism, with the goal of developing appropriate therapies in areas of high need and market potential.

The company is now looking to take this compound through the last steps of clinical development by partnering with either a larger pharma company or a dermatology specialty company.

The T_H2–atopic dermatitis connection

It is well established that activation of T_H2 cell–based CRTH2 by prostaglandin D_2 is a central mechanism in allergic and, more broadly, eosinophilic diseases such as atopic dermatitis and asthma[1].

A number of immune cells, including innate lymphoid cells and T_H2 cells, have a central role in the pathogenesis of eosinophilic disease. These cells respond to allergic and non-allergic stimuli by secreting key cytokines, such as interleukin 4 (IL-4), IL-5 and IL-13, that have a proven role in asthma and related conditions (**Fig. 1**).

Clinical validation for targeting T_H2 cells in these conditions has accumulated over the past decade. Regeneron's dupilumab, which targets IL-4 receptor α on T_H2 cells and is being developed in partnership with Sanofi, has shown promising results for treatment of asthma and atopic dermatitis. Another compound, Novartis's oral, selective, competitive and reversible CRTH2 antagonist QAW039 (fevipiprant), is also in clinical development for asthma.

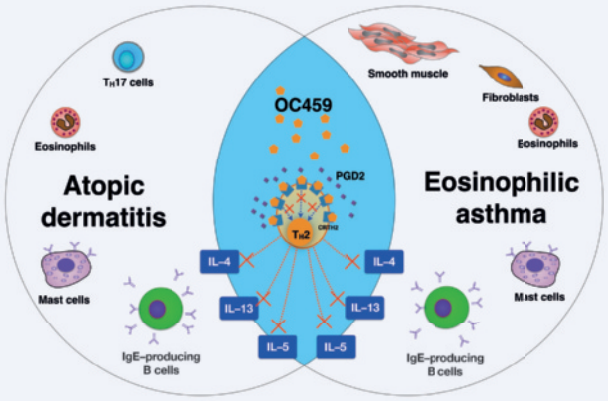

Figure 1: Several compounds are in clinical development targeting CRTH2, an important receptor molecule driving the effector cells behind atopic dermatitis, asthma and other allergic diseases.

Atopix has developed a pipeline of once-a-day, oral, small-molecule CRTH2 antagonists for T_H2-mediated disorders. Lead compound OC459 is in four clinical studies, including another phase 2 proof-of-concept trial in severe asthma. A next-generation compound, ATX2417, with improved potency is already in first-in-man trials in asthma.

According to Roy Pettipher, director of research at Atopix, the company's strategy is "to identify best-in-class CRTH2 antagonists as once-daily oral therapies for patients with allergic diseases where their pathology is driven by an overactive T_H2 immune response. The clinical success with anti–T_H2 cytokine antibodies has highlighted the potential of this approach in a market that is expected to exceed $10 billion in annual sales."

Atopic dermatitis lead

Atopix's lead compound, OC459, was the first CRTH2 antagonist to be shown to have clinical utility in eosinophilic asthma. Because of its mode of action, excellent drug-like properties and oral delivery regime, OC459 promises to have wider applicability and a stronger clinical profile than other therapies in the space.

In a phase 2b trial, OC459 was shown to substantially improve lung function in high-responder patients with a T_H2 high eosinophilic phenotype. So far the compound has exhibited an excellent safety profile in humans, and it is also effective at treating comorbid allergic diseases such as allergic rhinoconjunctivitis.

Atopix is testing OC459 in several clinical studies with highly targeted patient populations. OC459 has successfully completed long-term toxicology studies, and a commercially viable tablet formulation with an attractive once-a-day pharmacokinetic profile has been developed. These observations suggest that OC459 is safe and effective when administered once a day.

A follow-up compound to OC459, ATX2417, is under development for the treatment of asthma. This patent-protected compound has completed phase 1 trials and is being positioned to treat severe eosinophilic asthma.

Next steps

Atopix is backed by a strong board and a committed investor group, and the company is looking for partners to take its clinical development assets—OC459 and ATX2417—to the next level. Partnership setups could range from straightforward out-licensing of assets to a collaborative development deal with a large pharma company.

Tim Edwards, executive chairman of Atopix, stated, "With the imminent approval of anti-T_H2 biologics such as mepolizumab, it is an exciting time for the treatment of serious allergic diseases. We also expect some significant news flow over the next 20 months and believe Atopix is well placed to partner its once-a-day oral anti-T_H2 therapies with a leading player in the field in order to bring these much needed treatments to patients worldwide."

Reference

1. Pettipher, R. & Whittaker, M. *J. Med. Chem.* **55**, 2915–2931 (2012).

CONTACT DETAILS

Roy Pettipher, Director of Research
Atopix Therapeutics Ltd.
Abingdon, UK
Tel: +44 (0)1235 841522
Email: r.pettipher@atopixtherapeutics.com