



## **CRTH2 Antagonists in Asthma and Allergy**

## **Programme Objective**

- Develop potent antagonists of the G-protein coupled receptor CRTH2
- To validate multiple indications for such molecules in a range of allergic and inflammatory disorders
- To deliver a safe, oral once a day, drug molecule for use in adult and pediatric asthma
- To generate alternative molecules suitable for topical formulation for respiratory and other indications.

## **Summary**

**Oxagen has identified a number of potent antagonists of the CRTH2 receptor which are highly selective small molecular weight compounds with a range of physical properties enabling multiple administration routes to treat a range of allergic and inflammatory diseases in man. To date preclinical activity has been demonstrated in models of asthma, dermatitis and allergic conjunctivitis. The lead molecule OC000459 has completed Phase IIa clinical studies and has demonstrated efficacy in both asthma and allergic rhinitis. OC000459 is currently in a Phase IIb dose-range finding studies and the clinical data generated so far give confidence that this drug will be a safe and effective treatment for asthma and related conditions when administered once-a-day by the oral route. Other molecules in this and other series, all covered by Oxagen's patent estate are being developed for a range of other therapeutic indications including rhinitis, atopic dermatitis and allergic conjunctivitis.**

## **CRTH2: Validation in Asthma and Allergy**

The G-protein coupled receptor, CRTH2 (chemoattractant receptor-homologous molecule expressed on *Th2* cells), is one of two known receptors for the prostaglandin PGD<sub>2</sub>. The expression profile of this receptor is restricted to a number of key inflammatory cell types including Th2 cells, eosinophils, and basophils. Numerous studies have highlighted the PGD<sub>2</sub>/CRTH2 interaction in asthma and other allergic diseases, and an ever increasing body of evidence points to the potential therapeutic utility of CRTH2 antagonists.

Increasing evidence of the past few years indicates that CRTH2 plays a central role in key aspects of allergic pathology including:

- Recruitment and activation of Th2 cells, eosinophils and other leukocyte populations to sites of allergic inflammation
- Prevention of apoptosis of Th2 cells thereby impeding the resolution of allergic inflammation
- Production of Th2 cytokines such as interleukin 4, interleukin 5 and interleukin 13 leading downstream amplification of allergic disease
- Production of IgE
- Production of mucus
- Airway hyper-responsiveness

The role of CRTH2 in the allergic response has been reviewed by Pettipher and Hansel (2008).

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## **Discovery of CRTH2 Antagonists**

A “typical” industry standard screening cascade was established to screen compounds. This screening cascade employed a range of tests including receptor ligand binding, cell based efficacy, *in vivo* efficacy, and *in vivo* PK/PD. Chemical start points were identified via rationale design, based on knowledge of known CRTH2 ligands, or from screening a compound collection.

This campaign has delivered multiple lead series which have been included in a number of patent applications claiming chemical composition of matter and their use in inflammatory disorders. The program is still active and is pursuing novel structures in a number of series. To date, the program has delivered:

- OC000459 – a once a day oral development candidate for asthma and additional indications
- OC002417 – an extremely potent back-up molecule currently undergoing GLP toxicology studies
- A number of highly potent CRTH2 antagonists with physicochemical and ADMET properties suitable for topical administration for such disease as allergic conjunctivitis and atopic dermatitis