

## Allergic Inflammation

Asthma is a chronic disease affecting approximately 300 million people worldwide, with 180 000 deaths resulting annually from severe asthma attacks. Asthma is characterized by chronic inflammation in the airway, which consequently narrows more easily in response to a variety of triggers than the airway of a healthy individual. Triggers include allergens, tobacco smoke, air pollution, exercise, irritants, certain drugs, stress and strong emotions ([www.ginasthma.org](http://www.ginasthma.org), [www.who.int/topics/asthma/en/](http://www.who.int/topics/asthma/en/)), and exposure to these factors can result in an attack with symptoms such as coughing, tight chest, breathlessness or wheezing. These symptoms are caused by an increase in mucus secretion, bronchoconstriction and release of inflammatory mediators, which causes the airway to narrow, reducing the flow of air into and out of the lungs. Neither the cause of asthma nor the rapid increase in asthma prevalence around the world is understood. There is no cure for asthma, and current therapies rely mainly on inhaled corticosteroids and leukotriene inhibitors to prevent attacks, combined with bronchodilators to relieve the symptoms of an attack.

Tissue damage by long-term inflammation in the airways can lead to permanent changes in the airways, known as airway remodelling. Structural changes occur, causing airway obstruction that cannot be completely reversed, resulting in decreased lung function. Such changes include thickening of the airway wall with loss of epithelial organization, subepithelial fibrosis, increased vascularization, proliferation of fibroblast and myofibroblasts, goblet cell hyperplasia and smooth muscle cell hyperplasia and/or hypertrophy. Airway remodelling is related to the severity of asthmatic disease. The molecular mechanisms of such remodelling require investigation, in order to determine which events lead to structural changes that cause chronic asthma so that they may be targeted with anti-remodelling drugs. Consequently, our work focuses on the role of IL-4 receptor alpha (IL-4R $\alpha$ ) expression on various cells types such as T cells, B cells, macrophages and dendritic cells. The IL-4R $\alpha$  is known to play an important role in eliciting the Th2/type 2 inflammatory responses associated with allergy, as well as airway hyperreactivity, but its role in chronic asthma and airway remodelling remains to be elucidated.

## Selected Publications

Nieuwenhuizen, D. R. Herbert, N., A. L. Lopata, F. Brombacher (2007). CD4+ T Cell-Specific Deletion of IL-4 Receptor  $\alpha$  Prevents Ovalbumin-Induced Anaphylaxis by an IFN- $\gamma$ -Dependent Mechanism. *J. Immunol.* 179: 2758-65.

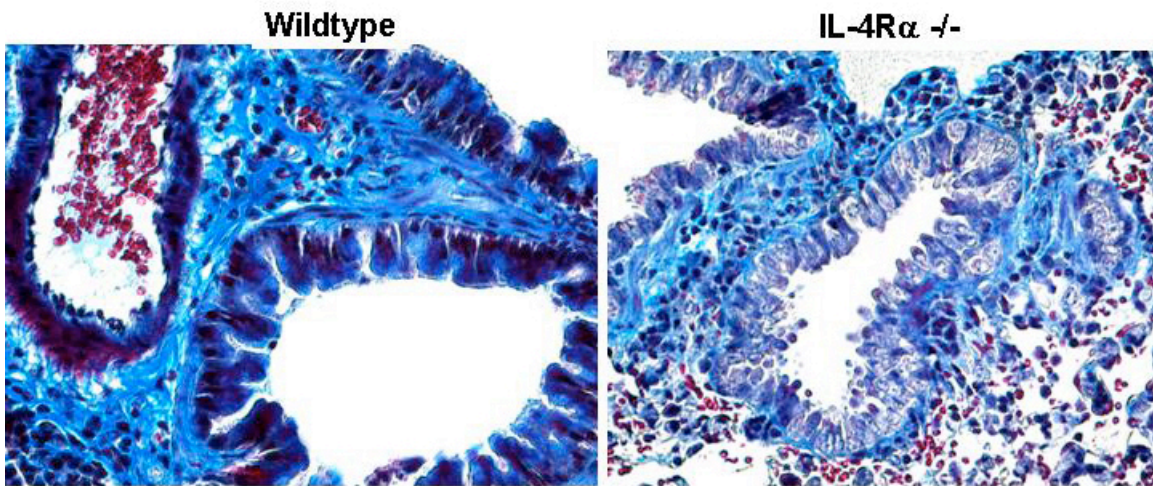
Nieuwenhuizen, N., A. L. Lopata, M. F. Jeebhay, D. R. Herbert, T. G. Robins, F. Brombacher (2006). The nematode *Anisakis*, hidden in fish, can cause occupational allergy. *J Allergy Clin Immunol*, 117:1098.

Kuperman, D.A., X. Huang, L. Nguyenvu, C. Hölscher, F. Brombacher & D.J. Erle (2005). IL-4 receptor signaling in Clara cells is required for allergen-induced mucus production. *J. Immunol.* 175:3746-52.

Okano, M., A. R. Satoskar, M. Abe, D. A. Harn, M. Okana, K. Nishizaki, Y. Takeda, T. Yoshino, F. Brombacher, AA. Satoskar. 2000. Interleukin-4-independent production of Th2 cytokines by nasal lymphocytes and nasal eosinophilia in murine allergic rhinitis. *Allergy*. 55:723-31.

Cohn, L., R. J. Homer, A. H. MacLeod, F. Brombacher, M. Mohrs, K. Bottomly. 1999. Th2 induced airway mucus production is dependent on IL-4R $\alpha$ , but not on eosinophils. *J. Immunol.* 162:6178-83.

Grünig, G., M. Warnock, A. E. Wakil, R. Venkayya, F. Brombacher, D. M. Rennick, D. Sheppard, M. Mohrs, D. D. Donaldson, R. M. Locksley, D. B. Corry. 1998. Interleukin 13 and interleukin 4 mediate the asthmatic phenotype through interleukin 4 receptor  $\alpha$ . *Science*, 282:2261-63.



CAB stain of lung airways from wild type mice (left) and IL-4R $\alpha$  deficient mice (right), showing the difference in collagen deposition (blue) in the airways after allergen challenge.