

## **College PhD Studentship in Respiratory Sciences**

**Studentship Number: MBSP-12/03**

**Primary Supervisor: Dr Yassine Amrani**

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**Institute of Lung Health, Department of Infection, Immunity and Inflammation**

**Co-supervisor: Pr. Christopher Brightling**

**Host Department: Department of Infection, Immunity and Inflammation**

**University of Leicester**

**Project Title: Novel therapeutic alternatives for the treatment of corticosteroid resistance in asthma**

### **Project Description:**

The precise molecular mechanism explaining the failure of 5-10% asthmatic patients to properly respond to corticosteroid (CS) therapy still remains unclear<sup>1</sup>. Finding novel therapeutic alternative to overcome inflammation-related steroid resistance in severe asthma is an unmet medical need. Using a cellular model of steroid resistance that was developed in our laboratory<sup>2-5</sup>, we have uncovered a number of different molecules induced by pro-asthmatic stimuli such as IRF-1 or GR $\beta$  that dramatically reduce the anti-inflammatory action of CS in airway structural cells. Our latest report showed that phosphatases also participate in mediating cytokine-associated steroid resistance. The purpose of this PhD studentship is to extend these observations by exploring novel therapeutic avenues to inhibit steroid-resistant genes. The student will focus on different compounds that can dissociate the transactivation function of corticosteroids from their beneficial transrepression function which mediates the vast majority of their anti-inflammatory actions, whereas transactivation has been associated with the unwanted side effects of corticosteroids<sup>6</sup>. We are looking for a highly motivated, hard working and exceptionally enthusiastic student who will obtain training in a range of state-of-the-art techniques applied to cells and tissues derived from healthy and asthmatic patients. Prior experience in cell culture, molecular biology, and protein analysis by ELISA and western blotting is strongly desirable.

### **Selected References**

1. Brightling CE, Gupta S, Hollins F, Sutcliffe A, Amrani Y. Immunopathogenesis of severe asthma. *Current pharmaceutical design* 2011;17(7):667-73.
2. Bhandare R, Damera G, Banerjee A, Flammer JR, Keslacy S, Rogatsky I, et al. Glucocorticoid receptor interacting protein-1 restores glucocorticoid responsiveness in steroid-resistant airway structural cells. *American journal of respiratory cell and molecular biology* 2010;42(1):9-15.
3. Tliba O, Amrani Y. Airway smooth muscle cell as an inflammatory cell: lessons learned from interferon signaling pathways. *Proc Am Thorac Soc* 2008;5(1):106-12.
4. Tliba O, Cidlowski JA, Amrani Y. CD38 expression is insensitive to steroid action in cells treated with tumor necrosis factor-alpha and interferon-gamma by a mechanism involving the up-regulation of the glucocorticoid receptor beta isoform. *Molecular pharmacology* 2006;69(2):588-96.
5. Tliba O, Damera G, Banerjee A, Gu S, Baidouri H, Keslacy S, et al. Cytokines induce an early steroid resistance in airway smooth muscle cells: novel role of interferon regulatory factor-1. *American journal of respiratory cell and molecular biology* 2008;38(4):463-72.
6. Adcock IM, Marwick J, Casolari P, Contoli M, Chung KF, Kirkham P, et al. Mechanisms of corticosteroid resistance in severe asthma and chronic obstructive pulmonary disease (COPD). *Current pharmaceutical design* 2010;16(32):3554-73.