ImmunoTools *special* Award 2017

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Androgen-dependent regulation of group 2 innate lymphoid cells: a new pathway to understand sex-differences in allergic asthma

During childhood, prevalence of asthma is higher in boys than in girls, but this tendency reverses during teenage years. Indeed, during adult life, the prevalence and severity of allergic asthma is higher in women than in men, suggesting an important role of sex hormones. However, the mechanisms underlying this sex bias are unknown. It is now well described that sex hormones can have pro- and anti-inflammatory effects, depending on the immune cell type they act on, and the hormonal dosage.

Allergic asthma is a complex disease defined by bronchial hyperactivity and respiratory tract inflammation characterized by a type 2 immune signature with a great production of cytokines such as IL-4, IL-5, IL-9 and IL-13. Group 2 Innate Lymphoid Cells (ILC2) have recently emerged as critical players in the initiation and the amplification of allergic responses due to their capacity to rapidly produce large amount of type 2 cytokines in response to allergen exposure. Indeed, when challenged with an allergen, mice lacking ILC2 failed to develop asthma. In the blood of patients suffering allergic asthma, the number of ILC2 is higher, as well as their type 2-cytokine production compared to non-allergic patients, suggesting a crucial role of ILC2 in the disease development and/or progression.

As a strong sex bias is observed in asthma incidence and severity, we thought to evaluate whether ILC2 could be influenced by sex hormones. We recently established that androgen signaling negatively controls ILC2 responses in mouse models (Laffont S, *J. Exp. Med.* manuscript in press). The aim of my PhD is now to understand further the underlying mechanisms implicated in the sex bias in ILC2 responses and to investigate whether sex hormones can also influence human ILC2s.

During the first part of my project, I will characterise and compare the ILC2 responses between women and men. ImmunoTools anti-human antibodies for flow cytometry will allow me to analyse ILC2 from healthy man and woman peripheral blood. I will determine if there are differences in ILC2 proportion, number and phenotype. I will set up *in vitro* culture model of human ILC2 to evaluate the impact of

sex hormones and/or hormone receptor inhibitors (estrogens and androgens) on their proliferation and effector functions in response to various cytokines. In these cultures, ILC2 proliferation, death (by AnnexinV staining), and cytokine production will be assessed. These *ex-vivo* and *in vitro* experiments will allow me to evaluate the direct effect of hormonal microenvironment on human ILC2 biological responses.

In the second part of this project, I will generate humanized mouse models to investigate the impact of sex hormones on ILC2 development and their functional responses to *in vivo* challenges with alarmin (e.g. TSLP).

This project will not only shed light on the mechanisms of the sex bias in allergic asthma, but could also lead to the development of new therapeutic approaches targeting androgen receptor to protect from ILC2-dependent pathologies. Indeed, administration of a weak androgen, with less virilising side effects, has shown beneficial effects in the treatment of allergic asthma in human.

ImmunoTools reagents will be key to providing an experimental answer to the scientific questions raised by this study, and to speeding the pace of our pre-clinical investigations. In addition, the findings from this research program should result in a publication in a peer-reviewed journal, and this would be my first paper as leading author. Needless to say, I should be pleased to acknowledge ImmunoTools' support in any publications and public presentations of the relevant data.

References:

Laffont S, Blanquart E, Savignac M, Cénac C, Laverny G, Metzger D, Girard JP, Belz GT, Pelletier Seillet C, and JC Guéry*. * co-authorship*
Androgen signaling negatively controls type 2 innate lymphoid cells
***J. Exp. Med**. (in press)*

ImmunoTools *special* AWARD for **Eve Blanquart** includes 25 reagents

anti-human antibodies for flow cytometry:

FITC - conjugated anti-human CD2, CD3, CD4, CD8, CD14, CD16, CD19, CD20, CD56, CD235ab, Annexin V

PE - conjugated anti-human CD11b, CD34, CD49d, Control-IgG1, Control-IgG2a, Control-IgG2b, Annexin V

PerCP - conjugated anti-human CD45

APC - conjugated anti-human CD4, Annexin V

anti-mouse antibodies for flow cytometry
FITC - CD45

recombinant human cytokines:

rh IL-2, rh IL-7, rh TSLP

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