

Progress report for Year 07/2007 to 07/2008.

Nod2 was the first reported susceptibility gene for Crohn's disease (CD), an inflammatory bowel disease that affects a growing fraction of the population in developed countries. *Nod2* is a member of the Nod-like receptors (NLRs), a family of intracellular microbial sensors that can alert the body of an infection. This has prompted investigators that CD could arise from a dys-regulated interaction between the commensal microflora (and possibly enteric pathogens) and the host, at the level of the intestinal mucosa. In my laboratory, we have studied the role of *Nod2* in bacterial detection for several years and, in the context of this grant from the CCFC, we aimed to get insights into how *Nod2* detects bacterial products, and how this might impact on the etiology of CD.

In this first year of support by the CCFC, we have studied how the structure of muramyl dipeptide (MDP; the bacterial ligand detected by *Nod2*) affects *Nod2*-mediated responses. In particular, we have analyzed *Nod2*-mediated responses to 37 MDP derivatives, which allowed us to identify the functional groups required for efficient detection. This approach has proven very useful, as we have been able, for the first time, to demonstrate that inflammatory responses mediated by MDP can be functionally decoupled from adjuvanticity (the capacity to mount an adaptive response with production of antibodies and effector cells). The impact of this observation might be important, as we will be able, in the next months, to engineer *Nod2*-dependent responses that rely only on one arm of the immune response (inflammation) or another (adaptive immunity). Consequently, our understanding of the role of *Nod2* in CD will significantly increase with respect to these questions.

In collaboration with the group of Dana Philpott (Department of Immunology, University of Toronto), we have investigated the role of *Nod2* in the polarization of the adaptive immune response *in vivo*, using *Nod2*-deficient mice. Our results, which have been published in December 2008 in the *Journal of Immunology* demonstrate that *Nod2* plays a critical role in the balance between Th1- and Th2-type immune responses following exposure to bacterial triggers. This observation is of importance given the fact that CD is known to be an inflammatory condition characterized by a Th1-skewed adaptive immune response. In particular, we conclude this article by the following:

“We hypothesize that intestinal macrophages and dendritic cells of patients carrying NOD2 mutations display an altered capacity for Th2 polarization. As a consequence, defective homeostatic Th2 immune polarization would be a critical determinant of the chronic Th1-polarized inflammation characteristic of CD. Therefore, we propose that Nod2 exerts a key role in the control of the Th2 polarization profile of resident myeloid cells of the intestinal lamina propria in homeostatic conditions, and that the rupture of this balance in Crohn's disease patients contributes to the increased susceptibility of the chronic intestinal inflammation. Therapeutic strategies aimed at targeting these resident myeloid cells to restore homeostatic Th2 polarization may prove useful for prophylactic and/or therapeutic treatment of Crohn's disease”.

Publications enabled by the grant on the period 07/2007 to 07/2008:

1. K Geddes, JG Magalhaes and SE Girardin (2009) *Unleashing the therapeutic potential of Nod-like receptors* **Nat. Rev. Drug Discov.** (in press)
2. JG Magalhaes, JH Fritz, L Le Bourhis, G Sellge, LH Travassos, T Selvanantham, SE Girardin, JL Gommerman and DJ Philpott (2008) *Nod2-dependent th2 polarization of antigen-specific immunity* **J Immunol** Dec 1;181(11):7925-35
3. S Benko, DJ Philpott and SE Girardin (2008) *The microbial and danger signals that activate Nod-like receptors* **Cytokine** Sep;43(3):368-73
4. LA Carneiro, LH Travassos and SE Girardin (2007) *Nod-like receptors in innate immunity and inflammatory diseases* **Ann. Med.** 39(8): 581-93
5. L Le Bourhis, S Benko and SE Girardin (2007) *Nod1 and Nod2 in innate immunity and inflammatory disorders* **Biochem. Soc. Trans.** 35(Pt 6): 1479-84