**McGill University Research Centre on Complex Traits - MRCCT**
**EXCELLENCE IN GENETICS & IMMUNOLOGY**
**SEMINAR SERIES**

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**Title**: "DNA double strand breaks in the Immune System: a dangerous game"

## Monday, March 27, 2017

## *Martin Amphitheater | Room 504, 4:00 PM*

*McIntyre Medical Sciences Building*

The immune system is the site of programmed DNA damages (DNAdsb) through the V(D)J recombination of Ig and TCR genes. These DNAdsb, when not properly repaired by the Non Homologous End Joining (NHEJ) pathway, result in the altered maturation of B and T lymphocytes ultimately resulting in Severe Combined Immune Deficiency (SCID). Cernunnos/Xlf, one of the NHEJ factors, is mutated in patients with SCID and microcephaly (Buck et al., 2006). Very surprisingly for a critical NHEJ factor, Cernunnos KO mice do not present with a major immunological phenotype other than a slight T and B cell lymphopenia and a bias in TCRVa and Ja usage, while their MEFs are strongly radiosensitive (Vera et al., 2013). We proposed that the RAG1/2 post cleavage complex (PCC) that tether DNA ends during V(D)J recombination may substitute for the XRCC4/Xlf filament in the absence of Xlf. Indeed, the concomitant defect in both Xlf and the RAG1/2 PCC results in profound V(D)J recombination and arrest of B and T cell maturation (Lescale et al., 2016).

These observations demonstrate a dual safeguard for the repair of DNAdsb (the most toxic DNA lesion) in developing lymphocytes and suggest that RAG2 directly participate in the DNA joining phase of the V(D)J recombination. This safety might be a general rule for other molecular mechanism that involve programmed DNA lesions such as meiosis, or gene rearrangement in the paramecia.

To better understand the functional relationships between NHEJ factors and the RAG1/2 complex during V(D)J recombination, we developed various murine models of gene inactivation (PAXX, XRCC4, Cernunnos/Xlf).

**Buck, D., L. Malivert, R. de Chasseval, A. Barraud, M.C. Fondaneche, O. Sanal, A. Plebani, J.L. Stephan, M. Hufnagel, F. le Deist, A. Fischer, A. Durandy, J.P. de Villartay, and P. Revy. 2006. Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. Cell 124:287-299.*

**Lescale, C., V. Abramowski, M. Bedora-Faure, V. Murigneux, G. Vera, D.B. Roth, P. Revy, J.P. de Villartay, and L. Deriano. 2016. RAG2 and XLF/Cernunnos interplay reveals a novel role for the RAG complex in DNA repair. Nat Commun 7:10529.*

**Vera, G., P. Rivera-Munoz, V. Abramowski, L. Malivert, A. Lim, C. Bole-Feysot, C. Martin, B. Florkin, S. Latour, P. Revy, and J.P. de Villartay. 2013. Cernunnos deficiency reduces thymocyte life span and alters the T cell repertoire in mice and humans. Mol Cell Biol 33:701-711.*

***This seminar is mandatory for Biochemistry Graduate students***

**LOCATION:** **McIntyre Medical Sciences Building, Room #504, 4:00 PM**

**HOSTED BY:** McGill University Research Centre on Complex Traits (MRCCT)