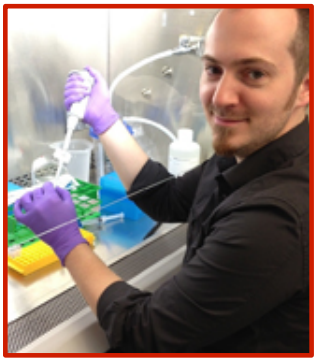
EXCELLENCE IN GENETICS & IMMUNOLOGY
SEMINAR SERIES



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Title: "Protective, non-protective and pathogenic CD4 T cell responses in Mycobacterium tuberculosis infection"

Tuesday, March 15, 2016

Karp Amphitheater | Room 501 | 12:00 PM

Goodman Cancer Research Centre

"The classic Th1 transcription factor and IFN-γ production by CD4 T cells are required for protection against *Mycobacterium tuberculosis* (Mtb) infection. We have previously shown that less-differentiated $Tbet^{low}CXCR3^{+}$ CD4 T cells are highly protective against Mtb infection despite a relatively reduced ability to produce IFN-γ. In contrast, $Tbet^{high}$ $CX3CR1^{+}$ $KLRG1^{+}$ CD4 T cells are terminally-differentiated cells that produce very high levels of IFN-γ but are short-lived and cannot migrate into the lungs and therefore do not contribute to control of Mtb infection. This has prompted us to reexamine to what extent IFN-γ contributes to overall CD4 T cell-mediated protection against Mtb and the role for Tbet in controlling CD4 T cell differentiation during Mtb infection. Here, we show that IFN-γ accounts for only ~30% of CD4 T cell-dependent cumulative bacterial control in the lungs over the first six weeks of infection, but >80% of control in the spleen. Moreover, selectively increasing the per capita IFN-γ–producing capacity of CD4 T cells by approximately 2 fold exacerbates lung infection and leads to the early death of the host, despite enhancing control in the spleen. We also find that the inhibitory receptor PD-1 is essential in Mtb infection to prevent the detrimental over-production of IFN-γ by CD4 T cells. Specifically, PD-1 suppresses the parenchymal accumulation of and pathogenic IFN-γ production by the $Tbet^{low}CXCR3^{+}$ subset of lung parenchymal CD4 T cells that otherwise mediate control of Mtb infection. These data argue the primary role for T cell-derived IFN-γ in Mtb infection is at extra-pulmonary sites, and the host protective subset of CD4 T cells requires negative regulation of IFN-γ production by PD-1 to prevent lethal immune-mediated pathology. We also show that while Tbet expression in T cells is essential for host survival of Mtb infection, Tbet is not required for the migration of CD4 T cells into the lungs of infected mice and instead promotes the generation of non-protective $KLRG1^{+}CX3CR1^{+}$ CD4 T cells that accumulate in the blood vasculature of the lung but do not enter the tissue parenchyma. Moreover, Tbet potently inhibits the generation of Mtb-specific $CD103^{+}$ $CD69^{+}$ Trm-like CD4 T cells in the lungs. Therefore, the superior protective capacity of less-polarized CD4 T cells against Mtb infection is likely due, at least in part, to several detrimental effects of high level Tbet expression on pulmonary CD4 T cell responses, and provide a mechanistic rational for limiting the degree of Th1 polarization during Mtb vaccination".

LOCATION: **Goodman Cancer Research Centre, Room #501, 12:00 PM**

HOSTED BY: DRS Judith MANDL and Silvia VIDAL