

Internship Proposal

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Project Title:

Improving IL-10-based immunotherapies

Level:

Master Student

Project Summary:

Interleukin (IL)-10 is a classical anti-inflammatory cytokine, with a key role in regulating immune responses. IL-10 is produced by many immune cells and acts on myeloid cells to suppress T cell responses. It is thus not surprising that IL-10 has garnered substantial clinical interest as an anti-inflammatory modulating agent. However, its therapeutic success has been limited, mainly due to the existence of several side-effects. Given the high potential of IL-10-based therapies, we became interested in understanding the mechanisms underlying these side effects. For that, our team has developed mouse models for time-controlled *in vivo* induction of therapeutic-related IL-10 levels. We showed that IL-10 unexpectedly reprogrammed bone marrow T cells to produce IFN- γ , driving emergency myelopoiesis. Therefore, we provided an explanation for the increase of IFN- γ and the hematologic alterations associated with IL-10 administration. More recently, our yet unpublished findings demonstrate that the bone marrow IL-10-reprogrammed T cells are senescent and infiltrate several non-lymphoid tissues, where they cause structural and functional alterations compatible with accelerated aging. Overall, our novel data place IL-10-reprogrammed T cells as key effectors of the IL-10 side effects.

Work to be developed by the student:

Aims: the aims of this project are to i) understand if the IL-10 reprogramming of T cells requires direct IL-10 signalling; and ii) provide a detailed molecular map of the alterations imposed by IL-10 elevation on T cells isolated from lymphoid and non-lymphoid tissues they infiltrate. These findings will ultimately contribute to refining the design of novel IL-10-based immunotherapies.

Main methodologies: For aim i) the student will take advantage of a novel mouse model



generated in our lab. In this model, the CD4 and CD8 T cells only lack the IL-10R, so these cells will not respond to IL-10 over-expression in vivo. In this mouse model, the hematopoietic process and main alterations to non-lymphoid tissues will be studied. This will involve flow cytometry, cell purification, organ harvesting and histology techniques. For aim ii) the student will apply RNA (including qPCR, and RNAseq) and protein (including ELISA, and Western Blot) analyses.

References:

1. Saraiva, M. & A. O'Garra, The regulation of IL-10 production by immune cells. *Nat Rev Immunol*, 2010. 10: 170.
2. Branchett, W.J., M. Saraiva, and A. O'Garra, Regulation of inflammation by Interleukin-10 in the intestinal and respiratory mucosa. *Curr Opin Immunol*, 2024. 91: 102495.
3. Saraiva, M., P. Vieira, and A. O'Garra, Biology and therapeutic potential of interleukin-10. *J Exp Med*, 2020. 217: e20190418.
4. Cardoso, A., et al., The Dynamics of Interleukin-10-Afforded Protection during Dextran Sulfate Sodium-Induced Colitis. *Front Immunol*, 2018. 9: 400.
5. Cardoso, A., et al., Interleukin-10 induces interferon-gamma-dependent emergency myelopoiesis. *Cell Rep*, 2021. 37: 109887.