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« T cell-Mediated Immune Tolerance » team
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Differentiation of regulatory T cell-subsets in the thymus

Regulatory T cells or "Treg" play a key role in the control of immune responses and thus prevent the development of autoimmune diseases and chronic inflammation. These cells also prevent rejection of the semi-allogeneic foetus by the maternal immune system and play an important role in repairing damaged tissues such as muscles and the nervous system. It turns out that the different functions of Tregs are provided by distinct subsets. Functional differentiation of Tregs occurs, in part, already in the thymus during their development.

The proposed thesis project focuses on the mechanisms involved in the differentiation of Treg subsets in the thymus, in particular on the involvement of different cytokines in this process. In order to identify the different Treg subsets we perform transcriptomic analyses of individual cells as well as flow cytometry. Using IL-2 and / or IL-15 deficient mice, we have demonstrated that these cytokines play important quantitative roles in the development of Tregs. Importantly, we have also observed that these cytokines play qualitative roles in this process: They influence differently the differentiation of Tregs into subsets. The proposed thesis project will study the *in vitro* and *in vivo* functional differences between Tregs that developed in wt or IL-2 and / or IL-15 deficient mice. The cellular origin of these cytokines in the thymus, a factor that will have important consequences on the different roles of IL-2 and IL-15, remains incompletely known. Using "conditionally deficient" mice in IL-2 or IL-15, we look for the source sources of these cytokines. Finally, the candidate will study subset-development in the human thymus.

A better understanding of the (intrathymic and peripheral) differentiation of the Treg subsets will later allow better designing of immunotherapy based on these cells, such as the experimental one we have developed for the prevention of chronic allograft rejection.

Team publications on this topic: (* Ph.D. / Master thesis students)

Thiault, N*., Darrigues, J*., Adoue, V., Gros, M*., Binet, B*., Perals, C., Leobon, B., Fazilleau, N., Joffre, O.P., Robey, E.A., van Meerwijk, J.P.M.#, and Romagnoli, P.# (2015). Peripheral regulatory T lymphocytes recirculating to the thymus suppress the development of their precursors Nature Immunology 16, 628–634.

Pasquet, L*., Douet, J.Y*., Sparwasser, T., Romagnoli, P., and van Meerwijk, J.P.M. (2013). Long-term prevention of chronic allograft rejection by regulatory T-cell immunotherapy involves host Foxp3-expressing T cells. *Blood* 121, 4303-4310.

Joffre, O.*, Santolaria, T.*, Calise, D., Al Saati, T., Hudrisier, D., Romagnoli, P., and van Meerwijk, J.P.M. (2008). Prevention of acute and chronic allograft rejection with CD4+CD25+Foxp3+ regulatory T lymphocytes. *Nature Medicine* 14, 88-92.

Joffre, O.*, Gorsse, N.*, Romagnoli, P., Hudrisier, D., and van Meerwijk, J.P.M. (2004). Induction of antigen-specific tolerance to bone-marrow allografts with CD4+CD25+ T lymphocytes. *Blood* 103, 4216-4221.

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