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VIII. Appendix

VIII.1 Publications in first (co-)author

- Bruck F, Belle L, Lechanteur C, De Leval L, Hannon M, Dubois S, Castermans E, Humblet-Baron S, Rahmouni S, Beguin Y, Briquet A, Baron F. *Bone marrow-derived mesenchymal stromal cells failed to prevent experimental xenogeneic graft-versus-host disease.* **Cytotherapy**; 2013; 15 (3), pp. 267-279

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VIII.2 Publications in co-author

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VIII.3 Oral Presentations at scientific meetings

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VIII.4 Posters presented at scientific meetings

- Belle L, Ehx G, Somja J, Binsfeld M, Hannon M, Caers J, Fransolet G, Beguin Y, Humblet S, Baron F. *Combination Of Regulatory T Cells and Rapamycin As Treatment For Experimental Chronic Graft-Versus-Host Disease.* **55th Annual Meeting of the American Society of Hematology**, New Orleans, LA, December 7-10, 2013.

- Belle L, Binsfeld M, Dubois S, Hannon M, Caers J, Briquet A, Menten C, Beguin Y, Humblet S, Baron F. *Prevention of murine sclerodermatous chronic Graft-versus-Host Disease by rapamycin*. **2013 BMT Tandem Meetings**, Salt Lake City, UT, February 13-17, 2013.

- Belle L, Bruck F, Foguenne J, Gothot A, Beguin Y, Baron F and Briquet A. *Imatinib and nilotinib do not prevent adhesion and migration of human CD34$^+$ cells in vitro and in immunodeficient mice.* **27th General Meeting of the Belgian Hematological Society**. Liège, January 27-28, 2012.

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IX. Thesis Abstract

Allogeneic hematopoietic cell transplantation (***allo-HCT***) remains the best treatment option for several hematological malignancies and some genetic disorders. Anti-tumoral efficacy of this approach is based not only on high dose chemo-radiotherapy given in the conditioning regimen, but also on immune-mediated graft-versus-tumor (***GVT***) effects, primarily mediated by donor T cells contained in the graft. Unfortunately, these donor immune cells can also target recipient tissues, causing a life-threatening complication of allo-HCT: the Graft-*versus*-Host Disease (***GVHD***). GVHD comprises two syndromes: acute GVHD (***aGVHD***), a deregulated inflammatory response causing skin, gastro-intestinal tract and/or liver damages, and chronic GVHD (***cGVHD***) generally occurring beyond day 100 after transplantation, and affecting virtually any tissue, and often inducing tissue fibrosis.

In recent years, significant progress has been achieved for aGVHD prevention. However, little improvement has been made for cGVHD treatment. Sclerodermatous cGVHD (***Scl-cGVHD***) occurs in up to 15% of patients who develop cGVHD and is one of the most severe forms of cGVHD. As there is a lack of efficient treatment for cGVHD, the first aim of this work was to find efficient drugs for scl-cGVHD.

However, reconstitution of a fully functional hematopoietic system is crucial for transplantation outcomes. Impacts of TKIs on hematopoietic stem cell engraftment and differentiation early after allo-HCT are unknown. We first demonstrated that imatinib and nilotinib had a similar impact on hematopoiesis *in vitro* and did not affect engraftment in immunodeficient mice. Since the PDGF receptor and TGF-β play a significant role in the fibrosing process occurring during scl-GVHD and their signaling pathways are inhibited by imatinib, we next assessed this TKI in a murine model of scl-GVHD. Unfortunately, imatinib failed to ameliorate scl-cGVHD in a severe murine model of scl-cGVHD despite it significantly inhibited PDGF-r *in vivo*.

In a third part, rapamycin was investigated both *in vivo* and *in vitro* for scl-cGVHD. Rapamycin inhibits conventional T cell activation and proliferation without inhibiting T_{reg} cells by acting via mTor. This immunosuppressant also inhibit fibrosis by acting via the PI3K/Akt signaling pathway, suggesting that rapamycin is a good candidate for scl-cGVHD. Rapamycin was able to increase survival of recipient mice by decreasing skin fibrosis and decreasing homing of effector T cells in GVHD target organs.