Transformation of normal cells into malignant cells is driven by activation of oncogenes and loss of function of tumor suppressor genes. Deregulation of the molecular networks controlled by these genes is essential for tumor cells to gain e.g. self-sufficiency in cell proliferation, increased replicative potential or insensitivity to growth inhibitory and differentiation-inducing signals.

Cells forming a tumor are not equally able to re-initiate the disease when introduced into an suitable host and this heterogeneity changes during disease progression and escape from anti-tumor therapy. Tumor progression also involves a complex dialog between tumor cells and cells of the microenvironment. Identifying the nodal molecular points at which cell-autonomous pro-oncogenic events and extrinsic signaling cues interact will likely help to tailor more adapted and efficient tumor therapies.

Figure 1: Anti-leukemic effects of treatment with calcineurin inhibitors cyclosporin A (CsA) and FK506 (Prog) in T-ALL bearing mice. Note reduction of leukemic blasts as compared to untreated (Unt) mice and re-initiation of normal hematopoesis in treated mice.
Our laboratory uses several, genetically-modifiable mouse models of acute lymphoblastic leukemia (ALL) and tumorgraft of human ALL cases to identify oncogenic pathways critical to maintenance of leukemias and to investigate if blockade of these pathways can synergize with chemotherapeutic agents currently used in ALL treatment. We found that the protein phosphatase calcineurin (Cn) is activated in lymphoid malignancies and demonstrated that it is critical to leukemia initiating cell activity in T-ALL (Medyouf et al. 2007; Gachet et al. 2013). NFAT factors are critical effectors of Cn in T-ALL cells and act through repression of major tumor suppressive pathways (Gachet et al. 2013 and unpbl; obs.). Cn activity also impinges upon the recycling of cell surface receptors critical to T-ALL biology (Passaro et al. under revision). We determined that a Frizzled receptor is responsible for Wnt/Ca2+ signaling in T-ALL cells, Cn being one of the effectors of this signaling pathway. Silencing of this receptor or its neutralization with monoclonal antibodies are anti-leukemic in vivo and sensitize T-ALL cells to chemotherapy (in preparation). Based upon our published observation that continuous TCR signaling impairs T-ALL maintenance (Dos Santos et al. Blood 2007), we have preliminary evidence for the anti-leukemic potential of anti-CD3 antibodies in mouse models of T-ALL. This analysis is now extended to T-ALL primagrafts. The gene encoding the chromatin remodeling factor Ikaros is frequently mutated in BCR-ABL-induced B-ALL. We generated the first mouse model showing synergy between BCR-ABL and IKZF1 loss-of-function (Virely et al. 2011). We identified the Ikaros-dependent transcriptomic signature in this model and found Ikaros deficiency to upregulate several tyrosine kinase receptors (RTK). Genetic studies demonstrated a critical function of an RTK receptor in BCR-ABL-induced B-ALL. In addition, we found that pharmacological inhibition of this RTK sensitizes BCR-ABL+ leukemic cells to the anti-leukemic activity of Nilotinib in vivo (in preparation). Extension of these observations to primagrafted Ph+ B-ALL is underway.