Dr. Hans-Willem Snoeck

Hematopoietic stem cells (HSCs) reside in the bone marrow (BM), are quiescent, can self renew, and generate all lineages of the hematopoietic system. Despite significant progress in our understanding of mechanisms involved in self-renewal, differentiation and quiescence, a coherent picture of how these mechanisms act in concert to regulate steady-state function and homeostatic responses of HSCs in vivo has not emerged yet. Furthermore, reliable renewal of HSCs *in vitro* has not been achieved, while there is overwhelming evidence that HSC self-renewal occurs *in vivo*. This implies that despite the identification of dozens of cytokines and of more than 200 genes that affect HSC function in knockout studies, and despite the publication of multiple studies on genome-wide expression and epigenetic signatures, significant gaps in our understanding remain. A particular gap is our understanding of the organellar cell biology of HSCs. HSCs rely predominantly on glycolytic ATP production, while many mature cells use mitochondrial oxidative phosphorylation (OXPHOS). Preferential use of glycolysis in stem cells suggests that mitochondrial respiration is more dispensable for HSCs than for progenitors, a notion supported by experimental data. These findings raise the question whether mitochondria play a role in HSCs that is not directly related to ATP production. In addition to ATP production, mitochondria are also required for several biosynthetic pathways and intermediary metabolism, apoptosis and intracellular calcium homeostasis. We show in our preliminary data that mitochondria are regulated in an exceptional fashion in HSCs, and that interfering with this regulation affects HSC function, at least in part by buffering intracellular calcium (Ca_{i}^{2+}), which we found to be strikingly low in HSCs compared to progenitors and non-hematopoietic cells. The goal of is the proposal is to better define regulation of mitochondria in HSC, its impact on Ca_{i}^{2+}, and HSC on maintenance, identity and function.