The liver is a central organ in the metabolism of nutrients, immune surveillance and toxin clearance. As such, liver dysfunction caused by toxic substances and infections can disturb important physiological processes and ultimately result in death if left untreated. Myeloid cells are vital in the immune response against threats and are key players to maintain and restore tissue integrity. Therefore, efforts to unravel the respective functions of myeloid cell subsets in liver inflammation could provide original concepts to restore homeostasis in this vital organ in a therapeutic setting. In this context, this PhD investigated the role of 2 myeloid cell populations during sterile and pathogen induced liver inflammation: Patrolling monocytes (PM) and live resident macrophages, the Kupffer cells (KCs).

First, we demonstrated that PMs perform a crucial protective role during APAP induced liver inflammation (AILI), the leading cause of acute liver injury in the western hemisphere. PMs stimulated the differentiation of hepatotoxic inflammatory monocytes (IM) into macrophages (Mf) with hepatoregenerative functions, which are essential to repair the damaged liver. This differentiation was mediated through the M-CSF receptor. Promoting this Mf differentiation through PMs might therefore be a promising new therapeutic target for the treatment of AILI.

Secondly, using a KC-depleter transgenic mouse generated by our lab (MCI, CMIM, Vrije Universiteit Brussel), Clec4f-DTR mice, we unveiled a protective role of KCs during Listeria monocytogenes infection. This food borne intracellular bacterium affects primarily immuno-compromised persons and pregnant women and can result in death and abortion. Mice lacking KCs had a decreased protective innate monocyte-derived dendritic cell response due to a blockage in differentiation from IM. Moreover, the absence of KCs resulted in inadequate adaptive CD8 T cell immune response, coinciding with reduced DC-poietsin production, a drop of the pre-cDC population and a reduction in conventional DC expansion. Consequently, these altered immune responses lead to an uncontrolled bacterial expansion pointing out the KCs as key initiators of immune responses during experimental listeriosis.

Finally, by addressing the fate of KCs in infected mice, we evidenced that IM engraft the liver and become KCs upon resolution of the infection.