Dendritic cells (DCs) are bone marrow-derived immune sentinel cells strategically distributed in peripheral tissues. These cells capture antigens in peripheral tissues and migrate to secondary lymphoid organs where they present the processed captured antigen on their MHC class II antigens. According to current paradigm DCs require initial activation to increase the expression of co-stimulatory molecules and the production of various pro-inflammatory cytokines (e.g. TNF-α, IL-12p75, IL-6), which in turn activate naïve T cells.

IL-12p75 is a heterodimeric cytokine, composed of a covalently linked p35 kDa and p40 kDa subunits. There is experimental evidence that DCs secrete IL-12p75 early during the innate immune response to Toll-like receptor (TLR) agonists that function as a bridge between the innate and adaptive immune systems. Furthermore, it has been shown that DCs produce IL-12p75 in response to bacteria/LPS, and that secretion of this cytokine skews T cell responses toward a T_H1-type cytokine pattern.

The work presented in this thesis challenges the idea that IL-12p75 acts like an early inducer of protective T_H1 immune responses against various infectious agents, especially where it concerns the notion that TLR agonists induce IL-12p75 secretion. The data presented in this thesis show that:

1) Stimulation of DCs with the TLR4 agonist LPS in the absence of T cells or T cell products does not result in IL-12p75 production.
2) Mice deficient in the IFN-γ gene do not secrete IL-12p75 in response to LPS.

3) Secretion of IL-12p40 is easily measurable and is independent of T cells or T cell products under *in vitro* and *in vivo* conditions, where IL-12p75 is undetectable.

4) Production of IL-12p75 is independent of IFN-γ when antigen-activated T cells are interacting with LPS-activated DCs.

5) LPS-activated DCs that have been termed “exhausted” and unable to secrete IL-12p75 can be induced to secrete this cytokine upon restimulation with antigen-activated T cells, but not by a combination of LPS with IFN-γ or naïve T cells.

Combined, these findings indicate that DCs secrete IL-12p75 in a tightly controlled process, in which antigen-presenting cells require help from non-naïve, antigen-activated T cells to secrete IL-12p75. Based on these data we propose that IL-12p75 does not represent a “bridge” that initiates the proinflammatory response to pathogens, but rather provide a positive feedback signal that can maintain an ongoing T_H1-dependent response once it has been established by other factors.

This thesis addresses a basic question: Is it IL-12p40 or IL-12p75 that is critical for the early host immune response following the encounter of DCs with microbial pathogens? We propose that it is the IL-12p40 and not IL-12p75 that is rapidly secreted by antigen presenting cells in response to TLR agonists during the initial innate immune response. Moreover, IL-12p40 secretion is an independent event that does not involve the production of the IL-12p75 heterodimer. Consequently, we suggest that IL-12p40 is not simply a

component of IL-12p75 or recently discovered IL-23, but an important molecule in its own right. Its secretion during the early host inflammatory response to pathogens plays an essential role in containing invading pathogens prior to recruitment of more elaborate arms of the adaptive immune system. Thus, we propose that IL-12p40 could be involved in early induction and secretion of IFN-γ during the innate immune response, which is independent of IL-12p75, which precedes the onset of the adaptive immune response.