7. CONCLUSIONS

Based on the experiments shown in this work, the following conclusions can be made about the role of Icsbp and Klf4 in the myeloid development:

- Klf4 is identified by this study as a novel macrophage maturation promoting transcription factor.

- Klf4 over-expression in myeloid progenitors leads to cell cycle arrest and macrophage differentiation, indicating that this protein acts as proliferation/differentiation switch.

- The mechanism of Klf4 activity in the macrophage differentiation involves direct activation of macrophage specific genes and suppression of granulocyte specific genes at an early stage of the development

- $p21^{Waf1}$ is a downstream target of Klf4, positively regulated by it.

- The over-expression of $p21^{Waf1}$ largely reproduced the effects of Klf4 over-expression, indicating that Klf4 function could be mediated through up-regulation of $p21^{Waf1.}$ However, the effects of $p21^{Waf1}$ over-expression were quantitatively milder than that of Klf4, indicating that Klf4 employs other, $p21^{Waf1}$ independent mediators.

- Presented results suggest a double role of $p21^{Waf1}$ in myelopoiesis: it controls the cell cycle and promotes macrophage maturation. These two roles can be decoupled and depend on the subcellular localisation of $p21^{Waf1}$: nuclear localization is necessary for the cell cycle inhibition, while differentiation induction is not strictly compartmentalized.

- Although similar in the expression pattern, responsiveness to extracellular stimuli and function in the myeloid development, Icsbp and Klf4 function through independent pathways.

- Mice with conditional deletion of Klf4 in hematopoietic tissues do not show aberrant hematopietic development, indicating that the lack of Klf4 can be compensated in normal myelopoiesis.

- Truncated Klf4 lacking its DNA binding region acts as dominant negative, blocking the differentiation of cells and showing the transforming potential of Klf4 in myeloid cells.

- Apart from its documented role in the development of macrophages and neutrophils, Icsbp plays an important role in the development of eosinophils. $Icsbp^{-/-}$ mice bare a reduced pool of eosinophil progenitor cells (EoPs) and impaired production of mature eosinophils, due to the reduced responsiveness of eosinophilic cells to their main growth factor Il-5 and reduced expression of Gata1, important transcription factor in defining the eosinophilic lineage