8. Summary

The main characteristic of chronic (myeloid) leukaemia is the development of progressive phases of the disease. The initial chronic phase is followed by the acceleration phase. The blast crisis, also named acute leukaemic phase or acute leukaemia, is the final phase of this disease which rapidly leads to the death of the patient.
What, in detail, triggers the switch of the phases and therefore causes the progression of the disease is not analysed yet. The knowledge so far is, that escalation of the disease is accompanied by genetic instability, which results in the activation of oncogenes and/or the inactivation of tumorsuppressor genes.

For pointed research of the progression of the chronic phase, the *Icsbp-/-* mice were used as an adequate mouse model. These Icsbp-deficient mice develop a CML-like MPD but an establishment of a blast crises is rather infrequent, so they only very rarely generate acute leukaemic phases.
The aim of the dissertation in hand was, by systematic deregulation of an oncogene respective of a tumorsuppressor gene, to gain a synergistic effect which leads to the development of leukaemias on the *Icsbp-/-* background.

In the first approach the oncogene and anti-apoptotic protein *Bcl-2* was overexpressed in the *Icsbp-/-* haematopoetic system. This setting did not show a cooperative effect between loss of Icsbp and overexpression of *Bcl-2* in order to generate an acute leukaemic phase. The frequency of leukaemias was very low. Furthermore the leukaemias indeed developed on the basis of the *Bcl-2* overexpression but seemed independent on the *Icsbp-/-* background. The long latency and low incidence of leukaemic cases led to the assumption that the genesis of the acute phase of leukaemias is, together with the *Bcl-2* overexpression, dependent on further genetic changes.

In the second approach Icsbp-deficiency was combined with the haploinsufficiency of Nf1, a tumorsuppressor and regulator of proliferation. This approach showed a synergistic effect between loss of Icsbp and deregulated tumorsupressor Nf1 in terms of the development of leukaemias: 46% of all *Icsbp-/-Nf1+/-* mice generated leukaemias. Myeloid leukaemias were most prominent, since 73,9% of all leukaemic *Icsbp-/-Nf1+/-* developed a leukaemia of the myeloid type. The malign transformation of the cells and therewith the change to the acute

leukaemic phase in the *Icsbp-/-Nf1+/-* mice was based on the additive reduction of the *Nf1*-level and the *Icsbp-/-* specific cellular background. That means, only the entire combination of the absent transcriptional activation of *Nf1* via Icsbp with the Nf1 haploinsufficiency and, additionally, with the *Icsbp-/-* based enrichment of the leukaemia initiating Lin^+ progenitorcell population leads to the development of leukaemias.

We demonstrated that, contrary to the current scientific opinion, a biallelic inactivation of the *Nf1* WT-allel, thus a LOH of *Nf1*, was not mandatory for the genesis of leukaemias but was dependent on the type of leukaemia. The majority of *Icsbp-/-Nf1+/-* mice with MPD like myeloid leukaemia did not show a biallelic loss of *Nf1* indeed.

A LOH of *Nf1* was predominant in leukaemis with high numbers of blastic cells, but showed a close correlation to different chromosomal abnormalities.

These results raised the question: Is the LOH of *Nf1* really mandatory for the development of leukaemias as an initiator of the malign transformation or is the LOH only a by-product due to enhanced proliferation and therefore increased genetic instability?

Altogether, loss of Icsbp combined with Nf1 haploinsufficiency created a synergistic effect in the *Icsbp-/-Nf1+/-* mice which caused an enhanced myelopoiesis in pre-leukaemic mice and finally the frequent development of mainly myeloid leukaemias.

Additionally, the *Icsbp-/-Nf1+/-* mice demonstrated to be an appropriate basic murine model to study the progression of chronic MPDs to leukaemias and to analyse the necessity of an LOH of *Nf1*.