6.3 Summary

The visual system, in particular the retino-collicular system of the mouse, serves as an excellent and easily accessible model to explore the molecular mechanisms underlying CNS development. In this context, members of the protein tyrosine phosphatase (PTP) superfamily seem to control several cellular processes during neural development, including proliferation, differentiation, migration, maturation and growth. Nevertheless, in contrast to their “opponents”, members of the protein tyrosine kinase family, the potential role of PTPs during CNS development is largely unknown.

The work at hand is subdivided into three main parts, which are presented in CHAPTERs 3-5.

These three Chapters are closely interconnected by the topics of (1) the clonal identification, (2) the expression pattern and (3) the functional importance of PTPs during retinal and collicular development. In order to analyze the functional significance of the PTPs, different knockout mouse strains were investigated.

The main results of each Chapter can be summarized briefly as follows:

**CHAPTER 3**, titled “Receptor protein tyrosine phosphatases are expressed by cycling retinal progenitor cells and involved in neuronal development of mouse retina” (Horvat-Bröcker et al., 2008), focuses on the potential role of six receptor-type PTPs (RPTPκ, RPTPJ, RPTPRR, RPTPσ, RPTPε and RPTPγ) during mouse retinal development. As systematically analyzed, using a combination of methods, e.g. quantitative real-time-PCR, *in situ* hybridization, immunohistochemistry and Western blotting, each RPTP exhibits a unique cellular expression pattern during critical periods of retinal histogenesis. Interestingly, the distinct mRNA and protein regulation pattern and the cellular expression of each RPTP correlate well with the onset of various cellular processes. In particular, during embryogenesis, the expression of all six RPTPs was observed in proliferative retinal progenitor cells (RPCs) and early postmitotic neurons, while in adulthood, each RPTP displays a more restricted cellular pattern. In addition, as revealed by Western blotting, we provide evidence for the developmental regulation of several RPTP isoforms. Furthermore, histological studies of RPTPβ/ζ knockout retinae revealed a disorganization of Müller glia fibers compared to wildtype retinae. This result gives a
first hint that RPTPβ/ζ might play an important role in establishing the phenotype of Müller glia during retinal development. In regard to these results, we suggest distinct roles for the investigated RPTPs, including their isoforms, during early retinogenesis as well as in the mature retina.

CHAPTER 4 comprises data from the publication titled "Protein tyrosine phosphatases expression during development of mouse superior colliculus" (Reinhard et al., 2009) and throws light on the clonal identification and expression pattern of both, intracellular PTPs and RPTPs, in the developing mouse superior colliculus.

Each of in total eleven PTPs exhibits distinct spatiotemporal regulation of mRNA and protein in the developing superior colliculus suggesting their versatile roles in neuro- and gliogenesis, as well as retino-collicular topographic mapping. Indeed, the study demonstrated the expression of several PTPs in collicular nestin-positive neural progenitor cells and RC-2-immunoreactive radial glia cells. Additionally, we showed an anterior-posterior expression gradient for RPTPJ in the Colliculus superior.

To sum up, CHAPTER 3 and CHAPTER 4 comprise very detailed descriptive results, which set the stage for further studies regarding the functional importance of PTPs within early CNS development.

CHAPTER 5, titled “Protein tyrosine phosphatase Meg2 deficient mice - A genetic tool to study eye development and glaucoma diseases?” (manuscript in preparation), summarizes data regarding the regulation, expression pattern and, most importantly, the functional relevance of the intracellular protein tyrosine phosphatase Meg2 (PTP-Meg2) during murine retinogenesis and eye development. In detail, we demonstrate a prominent expression of PTP-Meg2 in proliferative retinal progenitor cells (RPCs). When retinogenesis proceeds, PTP-Meg2 is restricted to amacrine and retinal ganglion cells (RGCs). Importantly, PTP-Meg2 deficient mice exhibit a “small-eye phenotype”, a hypocellular retina and a reduced proliferation capacity, which points to the functional importance of PTP-Meg2 during early retinogenesis. Furthermore, we provide evidence, that the differentiation of amacrine interneurons is delayed, while bipolar cell differentiation might be enforced in the PTP-Meg2 deficient retina.

Finally, using microarray analysis, we verified expression changes in several genes associated with an increased intraocular pressure (IOP). In accordance with these
findings, using *in vivo* tonometry, we demonstrate that adult PTP-Meg2 heterozygous animals develop an age-dependent elevated IOP. To our knowledge, this is the first report of a “glaucoma phenotype” in a protein tyrosine phosphatase deficient animal.

In conclusion, our results suggest that the protein tyrosine phosphatase Meg2 indeed plays different roles at defined time points of eye development. Furthermore, our data provide an important basis for future studies regarding the functional importance of PTP-Meg2 during CNS development.