**Introduction**

Neuroblastoma is a rare pediatric cancer, accounting for 15% of all deaths caused by cancer in children. This malignancy is genomically extremely heterogeneous, which results in a large clinical variability, ranging from spontaneous regression and long-term survival to aggressive, metastatic tumors with a fatal outcome in a high percentage of cases. Although research efforts have led to an increase in survival rates in low- and intermediate-risk patients, the survival rates of high-risk patients remain disconcerting, despite intensive, multimodal therapy.

To alleviate the burden of therapy, a more targeted approach is preferable. However, a comprehensive understanding of the genomic background of this disease is necessary, before new therapeutic targets can be implemented in the clinic.

In my research, we investigated the non-coding part of the neuroblastoma genome to find potential novel therapeutic entities, and improve outcome of patients.

**Summary**

In neuroblastoma, several protein coding genes are established as key players in the tumorigenesis and pathogenesis, such as ALK, MYCN and PHOX2B. These proteins regulate a plethora of other genes, however, little is known about their non-coding targets.

Based on the combination of RNA sequencing data of 497 primary tumor samples and model systems for MYCN, ALK and PHOX2B, we could demonstrate that each of these key neuroblastoma genes regulate a core set of lincRNAs, some of which were associated with certain disease stages or survival. Furthermore, we analyzed the data to find lincRNAs that modulate the effect, or are in charge of the regulation of these genes. Through a state-of-the-art computational workflow, various lincRNAs were identified as components in the networks surrounding these key genes. Both approaches allowed us to establish a core set of lincRNAs with a potential implication in neuroblastoma malignancy.

To evaluate the functional role of these lincRNAs, we focused on NESPR, a neuroblastoma specific lincRNA associated with PHOX2B and overall survival. NESPR (NEuroblastoma Specific Phox2B Regulatory rna) is located in the genomic region of PHOX2B and is a member of the noradrenergic core regulatory circuit (CRC) in charge of neuroblastoma cell identity. Through antisense oligonucleotide (ASO) mediated downregulation of NESPR, we evaluated its functional role and revealed a significant reduction of several neuroblastoma master regulators including PHOX2B, PHOX2A, DACH1 and ZNF536 while expression of CHD5 was significantly induced. These genes are members of the noradrenergic and mesenchymal CRC, regulating the neuroblastoma cell identity. Reduced levels of NESPR also resulted in a decreased growth rate and apoptosis. Using 4C-sequencing we could demonstrate a long-range interaction between the NESPR locus and the PHOX2B promoter, suggesting that the nuclear fraction of NESPR acts as a cis-regulator of PHOX2B expression.

Results from these functional experiments reveal a role for NESPR in neuroblastoma pathogenesis. However, further experiments are essential to confirm functionality of the other lincRNAs contained in our core set.