Exploring novel therapeutic strategies in neuroblastoma

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ABSTRACT

Neuroblastoma (NB) is the most frequently diagnosed extracranial tumour in children, which arises from transient embryonal tissue of the neural crest that fails to complete terminal differentiation into neurons. Even after completion of successful therapy, high risk neuroblastoma patients typically suffer from post-treatment induced toxicity which impacts on their ability to lead a normal life. Traditional protocols including chemotherapeutic and radiation therapy treatments are associated with toxic side effects due to a lack of specificity for malignant cells. Therefore, a rapidly expanding panel of targeted therapy agents are actively being explored. One example of targeted therapy is the use of small-molecule tyrosine kinase inhibitors (TKIs), a number of which have been developed and FDA approved as cancer therapeutics. Anaplastic lymphoma kinase (ALK) is one such TKI target in NB, where genetic analysis has identified *ALK* mutations in both sporadic and inherited NB, and at a higher frequency in relapsed cases. ALK TKIs are currently employed in adult ALK-positive cancer patients where they elicit good responses, prior to development of resistance.

In this thesis, we have focused on improving our understanding of known and novel molecular pathways involved in NB progression for further targeting (study I and III). We also tested a recently developed novel ALK TKI (study II) in a preclinical setting as an alternative strategy to treat NB patients in the future.

Keywords: Neuroblastoma, Anaplastic Lymphoma Kinase, Targeted therapy, ATR inhibition

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I. Van den Eynden J, Umapathy G, Ashouri A, Cervantes-Madrid D, **Szydzik J**, Ruuth K, Koster J, Larsson E, Guan J, Palmer RH, Hallberg B. Phosphoproteome and gene expression profiling of ALK inhibition in neuroblastoma cell lines reveals conserved oncogenic pathways. Sci Signal. 2018 Nov 20;11(557):eaar5680. doi: 10.1126/scisignal.aar5680

II. Cervantes-Madrid D, **Szydzik J**, Lind DE, Borenäs M, Bemark M, Cui J, Palmer RH, Hallberg B. Repotrectinib (TPX-0005), effectively reduces growth of ALK driven neuroblastoma cells. Sci Rep. 2019 Dec 18;9(1):19353. doi: 10.1038/s41598-019-55060-7

III. **Szydzik, J**, Lind, DE, Umapathy, G, Hallberg, B and Palmer, RH, Modulation of SUN2 phosphorylation downstream of ALK pathway identifies a role for ATR in neuroblastoma cell survival. Manuscript 2020

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