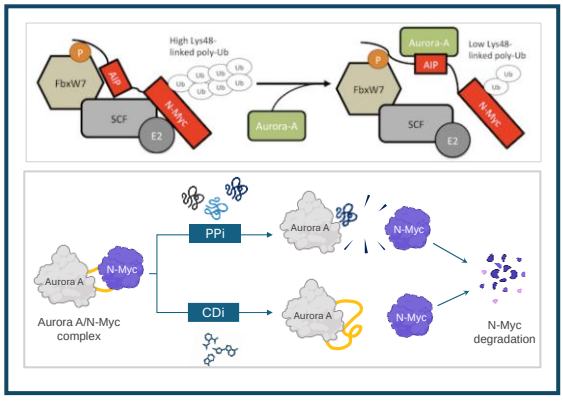
Project title: A two-pronged approach to target the Aurora-A/N-Myc complex in MYCN-amplified Neuroblastoma



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Description:

Neuroblastoma is a paediatric cancer of the peripheral nervous system. Elevated levels of N-Myc, due to genetic amplification of the MYCN oncogene, drive high-risk neuroblastoma. In these tumours, an excess of N-Myc is further promoted by its stable interaction with the mitotic Aurora-A kinase, which is required for the growth of MYCN-amplified cells. The physical interaction with Aurora-A sequesters N-Myc from proteolytic degradation, resulting in an accumulation of the latter. Targeting the "undruggable" Myc oncoproteins is a strong unmet need in paediatric cancer therapy. In MYCN-amplified neuroblastomas, disrupting the interaction between Aurora-A and N-Myc represents an alternative, promising approach to decrease N-Myc levels.

Aims:

We propose two complementary strategies, i.e. conformation-disrupting and protein-protein interaction inhibitors, to selectively target the Aurora-A/N-Myc complex. We will adopt a trans-disciplinary approach that recently led us to the identification of promising molecules acting as inhibitors of the Aurora-A/TPX2 and Aurora-A/N-Myc interaction. The experimental plan will encompass medicinal chemistry, structural biology, in vitro and in cultured cells assays, and investigations in animal models.

Expected results:

Through the innovative proposed approach to disrupt the Aurora-A/N-Myc interaction, we expect to obtain lead compounds ready to enter more extensive preclinical studies, and an in-depth understanding of the therapeutic value of targeting the complex. If successful, this project will provide a firm foundation for rigorously investigating pioneering drugs targeting the Aurora-A/N-Myc complex in clinical trials, for neuroblastoma treatment and other paediatric malignancies.

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