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Breaking the Evil Embrace between Auroraa and N-myc with Protein-protein Interaction Inhibitors

Simone Rossi [1], Corinne Sanglar [2], Florence Guilliere [1], Dalila Boi [3], Angela Tramonti [4], Roberto Contestabile [3], Alessandro Paiardini [3], Adriana Erica Miele [1]

[1] Université Claude Bernard Lyon 1, Villeurbanne, France

[2] CNRS, Villeurbanne, France

[3] Sapienza University of Rome, Rome, Italy

[4] CNR, Rome, Italy

Neuroblastoma is a pediatric cancer, characterized by a high grade of mortality, in which the amplification of MYCN oncogene determines a bad prognosis in 50% of cases. Our study wants to address a new strategy to target N-Myc, an intrinsically disordered transcription factor, difficult to inhibit. It has been shown that AuroraA kinase (AurKA) is able to bind N-Myc and to protect it from proteasomal degradation. This evidence highlights the AurKA/N-Myc interface as a new therapeutic target. The aim of my PhD project is to design protein-protein interaction inhibitors capable of disrupting this complex, therefore reducing neuroblastoma aggressiveness. In this respect, we compared the structures of protein kinase A (PKA) and AurKA in silico, and we took advantage of the physiological role of PKA inhibitor (PKI) to design fusion peptides between N-Myc and PKI. We synthetized and screened multiple sequences to obtain three peptides with nanomolar affinity for AurKA. We further characterized the 2D and 3D structure of these three by CD, FTIR and NMR. At present we are analyzing the AurKA/peptide complex structure by SAXS, MX and NMR. We have also performed in cell-NMR measurements to address the intrinsic instability of purified AurKA, a control of utmost importance to exclude false positive results. The best inhibitor will then be used to

create therapeutical peptidomimetics.