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Understanding the biological and clinical role of ecDNA in neuroblastoma

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Scientific Abstract:

There is a critical need for better clinical management of children with high-risk and relapsed neuroblastoma. Currently, amplification of *MYCN* remains the best-characterized genetic marker of risk in neuroblastoma and is one of the primary tumor features employed to determine patient treatment risk groups. Importantly, *MYCN* amplifications have been associated with a particularly poor overall survival. While *MYCN* amplifications in neuroblastoma can be found both within the linear genome and on circular extrachromosomal DNA (ecDNA), little is known about the clinical and biological effect of different types of *MYCN* amplifications. Here, we address this gap of knowledge by utilizing the two PIs' scientific expertise and synergistically combining large-scale genomics analyses with preclinical experimental evaluation of ecDNA pathology in neuroblastoma. Specifically, we propose to perform a comprehensive multi-omics examination of previously generated data from 796 patients with neuroblastoma to reveal the genomics, transcriptomics, and epigenomics features associated with ecDNA in these patients. All changes will be evaluated for statistical associations with clinical characteristics and targeted validation will be performed for key results using an independent clinical cohort. The genomics study will be complemented by utilizing *in vitro* and *in vivo* neuroblastoma disease models to provide insights into ecDNA-associated therapy resistance and clinical outcomes in response to standard-of-care chemotherapeutics. Overall, this project will elucidate the biological and clinical roles of ecDNA in neuroblastoma, potentially leading to improved clinical management of neuroblastoma and improved survival rates for children with neuroblastoma.

Lay Abstract:

Children with aggressive neuroblastoma tumors have poor rates of survival and cure despite intensive treatment, and better clinical management is needed. Increased number of copies of the *MYCN* gene is one of the best predictors of patients' survival, with higher *MYCN* copy number associated with worse overall survival. Recently, it was shown that *MYCN* can be amplified both within the chromosomes or outside the chromosomes on circular DNA molecules known as extrachromosomal DNA (ecDNA). Not much is known about the biological or clinical implications of these different types of *MYCN* amplifications in neuroblastoma. Importantly, different types of amplifications may be susceptible to different types of therapeutics. In this project, we will examine large datasets from neuroblastoma patients and scrutinize their molecular patterns in regard to potential clinical associations. Moreover, we will also screen laboratory cell line and tumor models to understand their response to commonly used drugs for treating children with aggressive neuroblastoma. Overall, the results from this study we provide a greater understanding of the biological and clinical roles of ecDNA in neuroblastoma, which may lead to improved success of neuroblastoma therapy and improved chances of survival for children with neuroblastoma.