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# Decoding the Role of the Long Non-Coding RNA PVT1 in Medulloblastoma

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## Scientific Abstract:

The proposed research will address an overarching and unsolved challenge in cancer biology: to develop effective treatments for MYC driven cancers, and Group 3 Medulloblastoma in particular, for which currently no therapy exists. MYC is the causal oncogene that drives 25-30% of all cancers, including a subset of Medulloblastoma, which has an extremely poor outcome. MYC is considered an undruggable candidate. We have previously challenged this paradigm by showing that MYC is often co-amplified with an adjacent long non- coding RNA, PVT1, and the latter acts as a master sensitizer of MYC protein in these cancer cells. We have recently pinpointed the mechanism of PVT1 mediated augmentation of MYC to a peptide encoded by a novel ORF, that we have named Firefox (FFX), formed by a circular RNA encoded by exon 2 of PVT1. This project aims to trace FFX in different subgroups of Medulloblastoma and understand how it contributes to the disease progression of MYC driven Medulloblastoma. Finally, we propose to exploit the dependence of MYC on FFX as a potential therapeutic avenue by illuminating the molecular mechanism by which FFX augments MYC expression in Medulloblastoma. This will help us to identify actionable targets that can render MYC unstable without having to target MYC directly, and hence will provide a strong therapeutic intervention for these cancer patients.

## Lay Abstract:

Medulloblastoma is the most common malignant childhood brain tumor. It is a highly heterogeneous cancer, comprising four subgroups: Sonic Hedgehog, Wingless, Group 3, and Group 4. Group 3 MB has the worst prognosis of all Medulloblastomas. Group 3 often exhibits amplification of chromosome 8q24, which contains the potent oncogene MYC. Unfortunately, patients with MYC-driven MB have few therapeutic options, since MYC is extremely refractile as a drug target. We have previously uncovered an important sensitizer of MYC, in form of PVT1. Inhibition of PVT1 effectively eliminates MYC protein, which in turn inhibits tumor growth. We have recently discovered that the critical unit in PVT1 is a 104 aa peptide, which we call Firefox (FFX), which augments MYC protein in cells. Here we propose to investigate the molecular mechanisms by which FFX controls MYC expression, and to design ways to target FFX which can, in turn, reduce MYC, and inhibit the cancer in these patients. This will uncover a novel way for new therapies for MYC driven MB patients.