

Pharmacological Inhibition of PAK1 for the Treatment of NF2-Associated Vestibular Schwannoma

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Neurofibromatosis Type 2 (NF2) is an autosomal-dominant genetic disorder characterized by loss of Merlin, a tumor suppressor in Schwann cells, resulting in pathognomonic bilateral vestibular schwannoma, among other complications. Depletion of Merlin results in pathologic elevation of p21-activated kinase 1 (PAK1), which promotes tumor cell proliferation, survival, and motility. Previous studies investigating the *Nf2^{fllox/fllox}; PAK1^{-/-}; Postn-Cre+* genetically engineered mouse model (GEMM) revealed that PAK1 genetic knockout in *Nf2*-cKO mice mitigated tumor size and preserved hearing. This study builds upon this previous work to identify efficacious therapeutic agents that target PAK1. *In vitro* dose response curves evaluated the efficacy of five PAK inhibitors in merlin-deficient immortalized Schwann cells (MS03). Dose response curves revealed variable IC50s among the five PAK inhibitors tested. Synergy screens revealed synergy between PAK inhibitors NVS-PAK1-1 or BGJ-398 and selumetinib, a MEK inhibitor FDA-approved for the treatment of NF1. Colony formation assays revealed robust inhibition with NVS-PAK1-1 in combination with VS6766, a RAF/MEK inhibitor currently being evaluated in clinical trial in other cancers. Western blot analysis revealed marked decrease in downstream effectors of PAK1, including phospho-ERK1/2 in cells treated with BGJ-398, NVS-PAK1-1, and PAKi plus selumetinib. Together, these findings suggest that inhibition of PAK1 and MEK pathways may be an efficacious therapeutic strategy for the treatment of NF2-associated vestibular schwannoma. Establishing reproducibility of these results in cells derived from human vestibular schwannoma is necessary to continue investigating pharmacological PAK1 and MEK inhibition. Further studies are needed to verify tolerability and therapeutic efficacy of PAK1 and MEK pharmacological inhibition *in vivo*.