

## **EPHA2 is a Potential Target for the Treatment of *NF2*<sup>-/-</sup> Vestibular Schwannoma**

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Neurofibromatosis type 2 (NF2) is an autosomal dominant cancer predisposition syndrome characterized by the development of bilateral vestibular (VS) and spinal schwannomas secondary to loss of heterozygosity of *NF2* in Schwann cells or their precursors. While these tumors are largely benign, they can cause considerable morbidity due to compromised auditory, vestibular, facial, and vertebral nerve function. This may result in deafness, vertigo, facial muscle weakness, chronic neuropathic pain, and even death. There are currently no pharmacotherapies for VS, and surgical resection remains the standard of care, which is associated with significant morbidity. Thus, there is an urgent need to develop pharmaceutical approaches to halt or reverse the progression of tumor growth in NF2 patients who develop VS. Our lab previously identified the receptor tyrosine kinase inhibitors brigatinib and dasatinib as potentially efficacious agents for the treatment of VS and demonstrated that both agents targeted the Ephrin A2 receptor (EPHA2). EPHA2 is a transmembrane receptor tyrosine kinase that is involved in cell contact-mediated motility, adhesion, and migration. Additionally, EPHA2 modulates axon guidance, and synaptogenesis in developing brain. Here we demonstrate that *EPHA2* expression is increased in *NF2*<sup>-/-</sup> Schwann cells and *NF2*<sup>-/-</sup> cancers. We identify ponatinib, a receptor tyrosine kinase inhibitor targeting *ABL1* that is FDA-approved for CML, as an additional agent that targets EPHA2. We demonstrate that ponatinib treatment impairs the viability of both human and murine *NF2*<sup>-/-</sup> Schwann cells *in vitro* and decreases EPHA2 protein expression. Accordingly, pharmacologic, and siRNA-mediated inhibition of EPHA2 also impaired the growth of human *NF2*<sup>-/-</sup> Schwann cells *in vitro*. Lastly, we demonstrate that both ponatinib and EPHA2 inhibition induce morphological changes in *NF2*<sup>-/-</sup> Schwann cells. Our findings suggest that ponatinib or the direct targeting of EPHA2 may be efficacious for the treatment of NF2-associated vestibular schwannoma. Future *in vivo* efficacy studies are warranted.