Supplementary Table 1: *SB* mutagenesis implicates Wnt/β-catenin signaling in neurofibroma and MPNST development in mice. Genes listed were identified in a murine *SB* screen for drivers of Schwann cell tumorigenesis, and all have known roles in canonical Wnt/β-catenin signaling. Listed are the percentage of neurofibromas or MPNSTs with an *SB* insertion within or near the gene listed, as well as the total number of tumors within a given gene.

Supplementary Table 2: QPCR primer sequences

Supplementary Figure 1: Human tissue microarray shows that C-MYC staining intensity increases with tumor progression. A. The intensity of C-MYC staining increases from benign neurofibromas to plexiform neurofibromas and is the greatest in MPNSTs. B. Example of C-MYC staining intensity.

Supplementary Figure 2: Overexpression of activated β-catenin and knockdown of *AXIN1* or *GSK3B* results in increased Wnt signaling and an induction of oncogenic properties in immortalized human Schwann cells. A-B. Expression of *CTNNB1S33Y* increases the expression of β-catenin, and known β-catenin co-activated genes *MYC, AXIN2, CCND1, LEF1*, and *BIRC5*. C. Immortalized human Schwann cells expressing shRNAs against *AXIN1* (iHSC1λ AXIN 84 and iHSC2λ AXIN 67) show a reduction in AXIN1 protein levels compared to cell lines expressing a non-silencing shRNA (NS GIPZ). D-E. Knockdown of *AXIN1* increases the expression of Wnt signaling outputs *MYC, AXIN2, LEF1, CCND1*, and *BIRC5* in both iHSC1λ.
and iHSC2λ cell lines. F. Knockdown of GSK3B in immortalized human Schwann cells (iHSC1λ GSK3B 91 and iHSC2λ GSK3B 90) results in a decrease in GSK3B protein levels compared to cells expressing a non-silencing shRNA (NS GIPZ). G-H. GSK3B knockdown increases Wnt signaling as shown by an increase in MYC, AXIN2, LEF1, CCND1, and BIRC5 expression. I. Immortalized human Schwann cells (iHSC1λ) transduced with shRNA against AXIN1 (AXIN 84) or GSK3B (GSK3β 91) show a decrease in expression level of AXIN1 and GSK3B transcripts, respectively, by QPCR compared to cells treated with a non-silencing shRNA (NS GIPZ). J. shRNA knockdown of either AXIN1 or GSK3B in iHSC1λ cells increases cell viability. K. iHSC1λ cell with knockdown of AXIN1 or GSK3B show an increase in soft agar colony formation. *p<0.05, **p<0.0001 unpaired T-test. Error bars represent SEM.

**Supplementary Figure 3: Knockdown of β-catenin or TNKS and overexpression of GSK3B results in decreased Wnt signaling in MPNST cell lines.** A-B. Knockdown of β-catenin in an NF1-associated MPNST cell line (S462-TY β-cat #23) and a sporadic MPNST cell line (STS-26T β-cat #22) results in a reduction in Wnt signaling as shown by reduced expression of MYC, AXIN2, CCND1, LEF1, and BIRC5. C-D. Knockdown of TNKS in an NF1-associated MPNST cell line (S462-TY TNKS #920) and a sporadic MPNST cell line (STS-26T TNKS #920) results in a reduction in Wnt signaling as shown by reduced expression of MYC, AXIN2, CCND1, LEF1, and BIRC5. E-F. GSK3B overexpression in S462-TY and STS-26T cell lines results in a decrease in the expression of Wnt pathway outputs MYC, AXIN2, CCND1, LEF1, and BIRC5 *p<0.05, **p<0.0001 unpaired T-test. Error bars represent SEM.
Supplementary Figure 4: Reduction of Wnt signaling by \( \beta\)-catenin knockdown or GSK3B overexpression reduces tumor growth in xenograft models. A. Reduction in \( \beta\)-catenin expression in the NF1-associated MPNST cell line (S462-TY) by shRNA (\( \beta\)-cat 23) results in a reduction in the rate of xenograft tumor growth compared to non-silencing shRNA (NS GIPZ) expressing cells. B-C. Tumors expressing a \( \beta\)-catenin shRNA are reduced in size and show a reduction in Ki67 positivity compared to NS GIPZ expressing cells. D. Overexpression of GSK3B in the sporadic MPNST cell line (STS-26T), results in a delay in xenograft tumor formation and reduction in the rate of xenograft tumor growth compared to cells expressing GFP/Luciferase (OE CTRL). E-F. Tumors overexpressing GSK3B are reduced in size and show a reduction in Ki67 positivity compared to cells expressing GFP/Luciferase (OE CTRL). Error bars represent SEM.