Bone morphogenetic protein-4

Bone morphogenetic protein-4 (BMP4) stimulates astroglial differentiation of GSCs and thereby reduces their self-renewal capacity. Exposure of GSCs to BMP4 may also sensitize these cells to TMZ. A recent phase I trial has shown that local delivery of BMP4 is safe, but a large variation in survival is seen in these treated patients and in features of their cultured tumors. We wanted to combine TMZ and BMP4 (TMZ + BMP4) therapy and assess the inter-tumoral variability in response to TMZ + BMP4 in patient-derived GBM cultures. A phase II trial could then benefit a larger group of patients than those treated with BMP4 only. We first show that simultaneous treatment with TMZ + BMP4 is more effective than sequential treatment. Second, when applying our optimized treatment protocol, 70% of a total of 20 GBM cultures displayed TMZ + BMP4 synergy. This combination induces cellular apoptosis and does not inhibit cell proliferation. Comparative bulk RNA-sequencing indicates that treatment with TMZ + BMP4 eventually results in decreased MAPK signaling, in line with previous evidence that increased MAPK signaling is associated with resistance to TMZ. Based on these results, we advocate further clinical trial research to test patient benefit and validate pathophysiological hypothesis [1)].

1)
Verploegh ISC, Conidi A, El Hassnaoui H, Verhoeven FAM, Korporaal AL, Ntafoulis I, van den Hout MCGN, Brouwer RWW, Lamfers MLM, van IJcken WFJ, Huylebroeck D, Leenstra S. BMP4 and Temozolomide Synergize in the Majority of Patient-Derived Glioblastoma Cultures. Int J Mol Sci. 2024 Sep 22;25(18):10176. doi: 10.3390/ijms251810176. PMID: 39337661; PMCID: PMC11432198.