# A new structured helical DPT-peptide containing a short canine adenovirus E4orf4PP2A$_1$, binding sequence inhibits a PI3K survival pathway in radioresistant human glioblastoma cell lines

Frank Ling
Paris

**Background:** Glioblastoma is the most common and most aggressive brain cancer in France, with around 2000 cases per year. The radioresistance of glioblastoma cells is a major problem in developing an effective therapy. Previous studies have established that numerous human cancers, including radioresistant human glioblastomas, require for their survival constitutive activation of the PI3K/Akt pathway. In this regard we have previously found that pharmacological inhibition of the PI3K/Akt pathway mediated by Ly29402 (PI3K inhibition) and A6730 (Akt inhibition) was toxic for radioresistant U87G and SF763 cells, but had no effect on non-transformed human DHF fibroblasts. In this context, the PP2A family of Ser/Thr protein phosphatases is a central regulator of cell homeostasis that counteracts the aberrant oncogenic PI3K survival signal. Importantly, the trimeric ABαC holoenzyme, named PP2A1, specifically counteracts the aberrant oncogenic constitutively activated PI3K survival signal. In this regard, we recently reported that PP2A pharmacological activation mediated by the sphingolipid analog FTY720 downregulated the constitutively active PI3K/Akt pathway involved in survival of radioresistant human glioblastoma U87G cells.

**Methods and results:** Using our peptide-based DPT technology we have rationally designed a new PP2A named DPT-E4orf4$_{23\text{-}38}$, which combines the HIV-1 Tat shuttle plus the canine adenoviral type 2 E4orf4$_{23\text{-}38}$ PP2A$_1$-binding sequence. This new chimeric sequence inhibited survival of U87G and SF763 cell lines. DPT-E4orf4$_{23\text{-}38}$ also inhibited Akt-phosphorylation (ser473) and decreased growth of U87G and SF763 cells. Finally, DPT-E4orf4$_{23\text{-}38}$ decreased growth of X-irradiated (2Gy) senescent U87G cells.

**Conclusion:** Taken together, our results suggest that DPT-E4orf4$_{23\text{-}38}$, alone or combined with irradiation, should be clinically evaluated as a potential therapeutic molecule for PI3K-dependent, radioresistant and irradiation-induced senescent human glioblastomas.