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The impact of a protein phosphatase 2A inhibitor on glioblastoma and neurodegeneration

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INTRODUCTION & AIM

Protein phosphatase 2A (PP2A) is a potential target for treating inflammation, neurodegeneration, and cancer. Reduced levels of PP2A are associated with neurodegeneration, along with increased levels of endogenous PP2A inhibitors. In cancer treatment, PP2A is a tumor suppressor which inhibition hyperactivates multiple oncogenic signalling pathways and could be lethal to cancer cells particularly in combination with other anticancer drugs.

PP2A inhibitor (LB-100)

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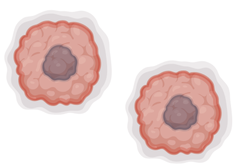


→ mitotic catastrophe

senescent cancer cells

LB-100 + adavosertib

LB-100 + paclitaxel ?

LB-100 + doxorubicin

METHOD

IN VITRO: The effects of PP2A inhibitor (LB-100) alone and in combination with either Wee1 kinase inhibitor (adavosertib), paclitaxel, and inhibitor of topoisomerase II (DOX, doxorubicin) were assessed on primary human glioblastoma grade 4 cells.

Methodology: imaging with the ImageExpress PICO, real-time quantitative cell analysis with xCELLigence, and cell death induction analysis with flow cytometry.

IN VIVO: C57BL/6J wild type mice received intraperitoneal injections of LB-100 at a dose of 1.5 mg/kg on days 1, 3, and 5, repeated in 5 cycles, for the novel recognition test.

RESULTS & DISCUSSION

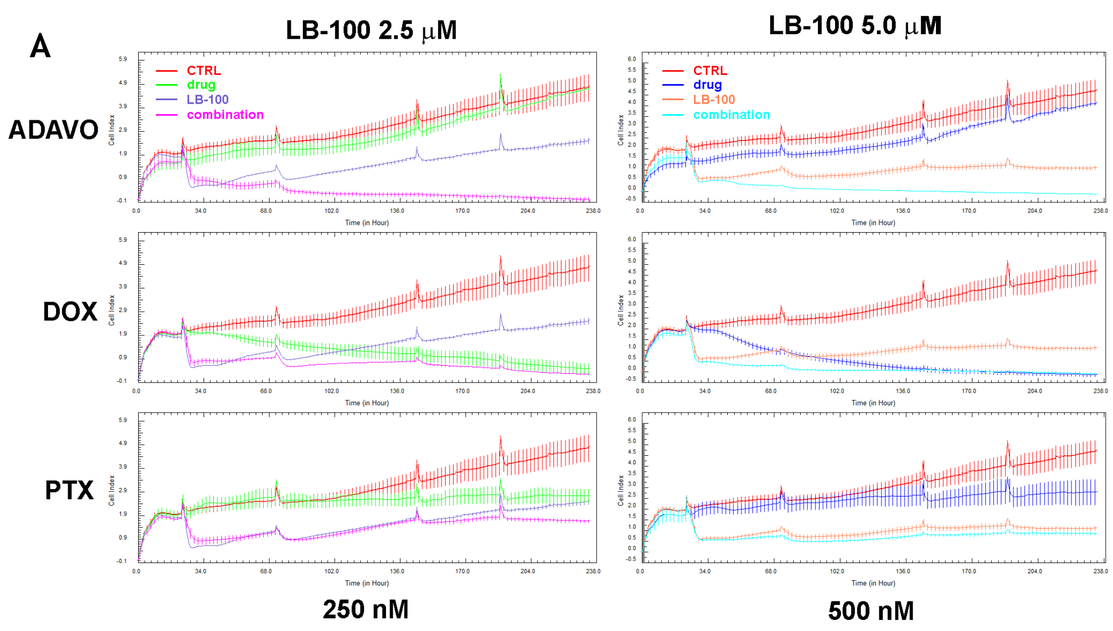
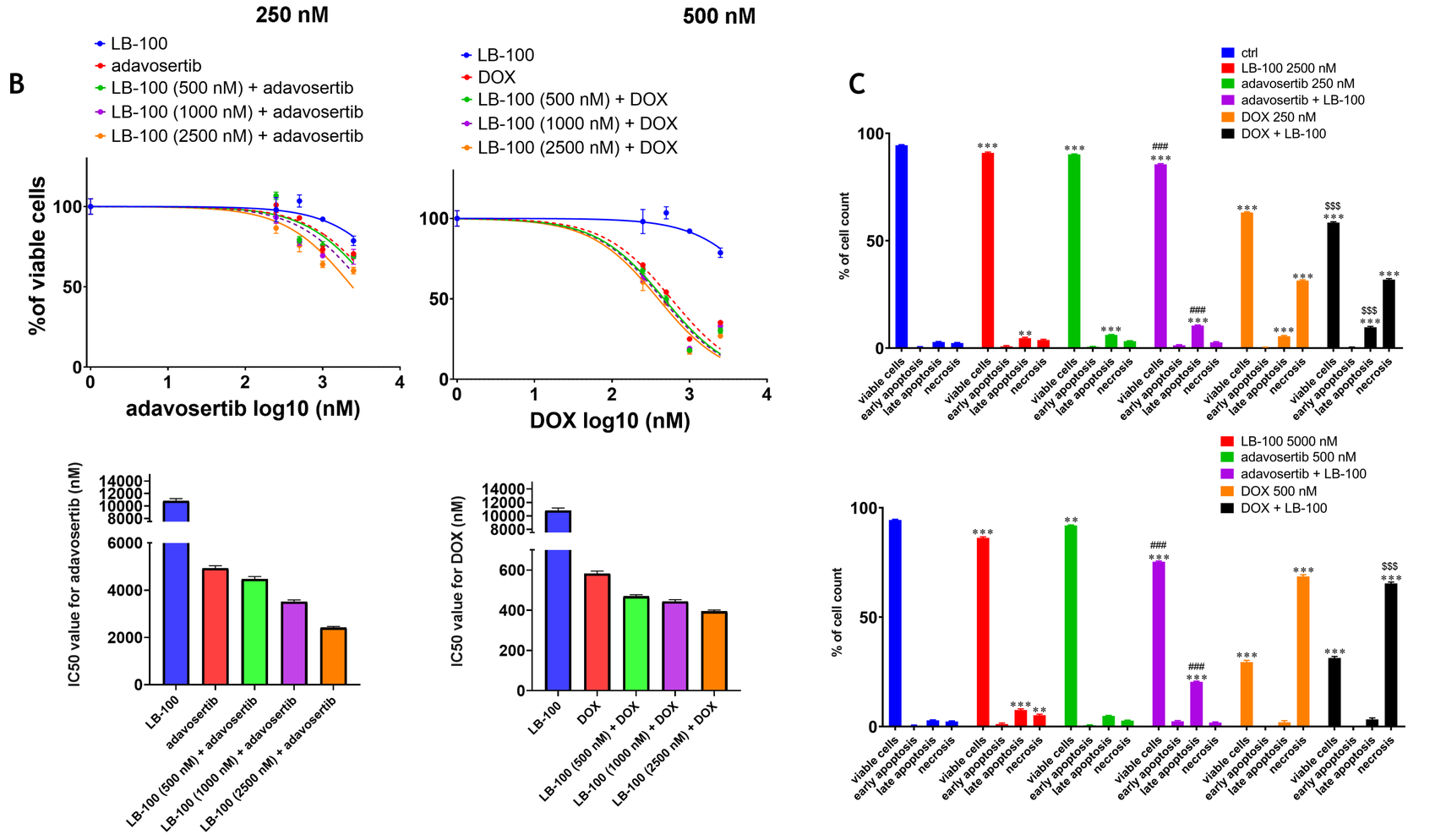


Fig 1. A) LB-100 is synergistic with adavosertib and DOX in glioblastoma primary culture. B) LB-100 decreases IC50 value for adavosertib and DOX in concentration-dependent manner. C) Combination of LB-100+adavosertib increases the late apoptosis, and LB-100+DOX increases the late apoptosis and necrosis.



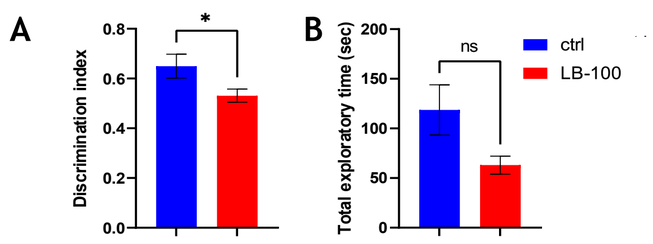


Fig 2. Novel object recognition test on C57J wild type mice. A) Discrimination index based on exploratory time. Mice injected with saline (ctrl) showed novel object preference, while mice injected with LB-100 showed no preference. B) Total exploratory time, in seconds. The results from mice injected with saline and LB-100 showed marginally significant difference.

CONCLUSION

Our initial findings indicate that glioblastoma cells were sensitive to LB-100, while its combinations with adavosertib and doxorubicin were synergistic.

Additionally, continuous treatment with LB-100 for 5 weeks resulted in impairment of short-term memory.

It is important to investigate the central effects of PP2A inhibition and to assess whether its anticancer potential interferes with memory and cognition.

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