



# Pharmacological Targeting of NFkB and Topoisomerase II are Synergistic for Treatment of Proneural Glioma Cells.

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## Introduction

Molecular-based personalization of malignant glioma therapies has the potential to improve survival. We recently discovered a transcriptional network that drives gene expression in Proneural gliomas, a molecularly defined subtype of malignant gliomas.<sup>1,2</sup> NFkB is a prominent transcription factor identified on this network.<sup>1</sup> Proneural gliomas have characteristic high levels of Topoisomerase II (TOP2), and we found that Proneural mouse gliomas are susceptible to TOP2 targeting with etoposide treatment by convection-enhanced delivery.<sup>2,3</sup> In order to enhance efficacy of etoposide in this setting, a high-throughput in vitro screening of DFA-approved drugs targeting transcription factors from the Proneural transcriptional network was performed in combination with etoposide.

## Methods

Dose response curves were established for individual agents, followed by 4x4 dose combinations for the two agents on a screening phase, and 10x10 drug combinations on a subsequent confirmatory experiment. Each concentration had 6 replicates. All experiments were performed on an automatic plating, treatment and viability reading system. Synergy was calculated using the excess of Bliss method. Experiments were performed on previously established mouse Proneural glioma cell lines.<sup>4</sup>

## Results

A drug known to target KfB had no therapeutic effect on its own, but was highly synergistic in combination with etoposide in Proneural cell lines. To investigate whether TOP2 was involved in the encountered synergy, we tested the combination the NFkB targeting drug and MST-16, a TOP2 inhibitor, in which case therapeutic synergy was also observed.

## Conclusions

Pharmacological modulation of the transcriptional network might constitute a strategy for personalizing and improving the efficacy of malignant glioma therapies. Treatment with NFkB and TOP2 targeting drug combinations are effective and synergistic on Proneural glioma cell lines. Further studies are underway to investigate the roles of NFkB and TOP2 on the observed therapeutic synergy, and to test this effect in vivo.

## Learning Objectives

Personalizing glioma therapies using molecular-based treatment selection.

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## References

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