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Aptamer-based RNA-bio-drugs for the combined therapy of GBM

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Abstract. This paper describes a novel combined approach to targeting GBM with multiple RNA-based therapeutics. Overall, the results demonstrate the good potential of a smart safe and clinically applicable combined regimen for the treatment of glioblastoma, opening up a new avenue in the treatment of this aggressive disease.

Key words: cancer, aptamer, RNA therapeutics, targeted delivery.
Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.
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Glioblastoma multiforme (GBM) is the most common aggressive and incurable brain cancer in adults, with a very dismal prognosis for patients [1]. Nucleic acid therapeutics, including siRNAs and miRNAs/antimiRs, are emerging highly promising molecules for the precise treatment of refractory aggressive GBM. However, the clinical use of oligonucleotide-based therapies required development of precise and safe targeted cell delivery strategies. In the last decade, nucleic acid aptamers-synthetic RNA/DNA molecules acting as high affinity ligands – or antagonists of their selected target – have provided very promising carriers for therapeutic oligonucleotides [2]. Here we describe a novel combinational approach to target GBM with multiple RNA-based therapeutics. We designed two conjugates containing two aptamers that bind to, and inhibit, the receptor tyrosine kinases, Axl and PDGFRβ, as targeted carriers of therapeutic RNAs inhibiting two key players of GBM (STAT3 and miR-10b) [3]. We have demonstrated that both the conjugates hamper GBM cell growth and migration and effectively and specifically prevent patient-derived glioblastoma stem cell (GSC) function and expansion [4, 5]. MRI spectroscopy was used to prove the effectiveness of innovative drugs based on aptamers in vivo. Most importantly, we demonstrate the therapeutic efficacy of such molecules *in vivo* in patient-derived GBM models and we show that the developed chimeras synergise both *in vitro* and *in vivo*. Collectively our results highlight the potential of a smart, safe and clinically translatable combined regime for GBM, opening a new path in the treatment of this aggressive disease.

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