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1: [Int J Cancer](#). 2008 Sep 9. [Epub ahead of print] [Related Articles](#), [Links](#)



**Cure of established GL261 mouse gliomas after combined immunotherapy with GM-CSF and IFNgamma is mediated by both CD8(+) and CD4(+) T-cells.**

[Smith KE](#), [Fritzell S](#), [Badn W](#), [Eberstål S](#), [Janelidze S](#), [Visse E](#), [Darabi A](#), [Siesjö P](#).

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We were the first to demonstrate that combined immunotherapy with GM-CSF producing GL261 cells and recombinant IFNgamma of preestablished GL261 gliomas could cure 90% of immunized mice. To extend these findings and to uncover the underlying mechanisms, the ensuing experiments were undertaken. We hypothesized that immunizations combining both GM-CSF and IFNgamma systemically would increase the number of immature myeloid cells, which then would mature and differentiate into dendritic cells (DCs) and macrophages, thereby augmenting tumor antigen presentation and T-cell activation. Indeed, the combined therapy induced a systemic increase of both immature and mature myeloid cells but also an increase in T regulatory cells (T-regs). Cytotoxic anti-tumor responses, mirrored by an increase in Granzyme B-positive cells as well as IFNgamma-producing T-cells, were augmented after immunizations with GM-CSF and IFNgamma. We also show that the combined therapy induced a long-term memory with rejection of intracerebral (i.c.) rechallenges. Depletion of T-cells showed that both CD4(+) and CD8(+) T-cells were essential for the combined GM-CSF and IFNgamma effect. Finally, when immunizations were delayed until day 5 after tumor inoculation, only mice receiving immunotherapy with both GM-CSF and IFNgamma survived. We conclude that the addition of recombinant IFNgamma to immunizations with GM-CSF producing tumor cells increased the number of activated tumoricidal T-cells, which could eradicate established intracerebral tumors. These results clearly demonstrate that the combination of cytokines in immunotherapy of brain tumors have synergistic effects that have implications for clinical immunotherapy of human malignant brain tumors. (c) 2008 Wiley-Liss, Inc.

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