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CANCER STEM CELLS

## Direct Orthotopic Transplantation of Fresh Surgical Specimen Preserves CD133<sup>+</sup> Tumor Cells in Clinically Relevant Mouse Models of Medulloblastoma and Glioma

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### Abstract

Recent identification of cancer stem cells in medulloblastoma (MB) and high-grade glioma has stimulated an urgent need for animal models that will not only replicate the biology of these tumors, but also preserve their cancer stem cell pool. We hypothesize that direct injection of fresh surgical specimen of MB and high-grade glioma tissues into anatomically equivalent locations in immune-deficient mouse brains will facilitate the formation of clinically accurate xenograft tumors by allowing brain tumor stem cells, together with their non-stem tumor and stromal cells, to grow in a microenvironment that is the closest to human brains. Eight of the 14 MBs (57.1%) and two of the three high-grade gliomas (66.7%) in this study developed transplantable (up to 12 passages) xenografts in mouse cerebellum and cerebrum, respectively. These xenografts are patient specific, replicating the histopathologic, immunophenotypic, invasive/metastatic, and major genetic (analyzed with 10K SNP array) abnormalities of the original tumors. The xenograft tumor cells have also been successfully cryopreserved for long-term preservation of tumorigenicity, ensuring a sustained supply of the animal models. More importantly, the CD133<sup>+</sup> tumor cells, ranging from 0.2%–10.4%, were preserved in all the xenograft models following repeated orthotopic subtransplantations *in vivo*. The isolated CD133<sup>+</sup> tumor cells formed neurospheres and displayed multi-lineage differentiation capabilities *in vitro*. In summary, our study demonstrates that direct orthotopic transplantation of fresh primary tumor cells is a powerful approach in developing novel clinical relevant animal models that can reliably preserve CD133<sup>+</sup> tumor cell pools even during serial *in vivo* subtransplantations.

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**Key Words.** medulloblastoma, glioma, orthotopic xenograft model, cancer stem cell

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