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## Tumor Biology 18: Animal Models of Human Cancers 3: Central Nervous System and Imaging Abstract #2732

# Isolation of cancer stem cells from a mouse model of brain tumor

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Recent reports describing the existence of cancer stem cells in solid tumors, including primary brain tumors, offer important insights into tumor pathogenesis and may provide opportunities to develop more efficacious and less toxic therapies for the treatment of cancer. Key to those efforts will be the opportunity to model this important aspect of tumor pathology in mice. We sought to determine if there was evidence of cancer stem cells in a mouse model of oligodendroglioma, an important malignancy of the central nervous system. We have isolated tumor-initiating cells from S100beta-verbB transgenic animals in which spontaneous brain tumors, oligodendroglioma, arise at high frequency (Weiss et al, Cancer Research, 2003). In vitro, these cells grow as tumor spheres and continue to proliferate after multiple passages in defined medium in the absence of added growth factors. When plated at clonal density, approximately 30% of the cells gave rise to secondary spheres, indicating self-renewal capacity of tumor stem cells. In addition, varying percentages of cells within tumor sphere cultures express cell-surface antigens such as CD133, CD44 and BCRP1, which are associated with stem cells. Under differentiation promoting conditions, the vast majority of cells express markers of early oligodendrocytes, while a small percentage of cells express markers of astrocytes and neurons. However, their differentiation is abnormal and they never express markers of terminally differentiated oligodendrocytes, such as myelin basic protein, consistent with their tumor origin. In addition, these cells are capable of initiating a new tumor in immunosuppressed mice even when injected in small numbers (100-10,000 cells) giving rise to tumors that replicate the original tumor type. We were able to isolate tumor sphere forming cells after multiple rounds of serial injections in immunosuppressed mice. These data indicate that this mouse brain tumor model faithfully replicates important aspects of the pathobiology of human brain tumors and may provide a useful in vivo model in which novel therapeutic approaches, including those devised to target tumor stem cells, can be developed. We are in the process of isolating pure populations of cells that express specific stem cell markers and testing their abilities to initiate new tumors in vivo. In addition, we are also investigating the sensitivity of these cells to clinically relevant chemotherapeutic agents. (This work was supported by the Betz Foundation grant to MAI and Oligo Brain Tumor Fund from NBTf to KY).

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