



“A role of a transcription factor, FoXM1, in cancer stem cells in pediatric brain tumors”

Despite the dramatic improvements in the outcome of other childhood cancers in the last decades, brain tumors remain the leading cause of death in the pediatric oncology. Malignant brain tumors are composed of heterogeneous cell populations. Recent investigations, including our own, have identified a stem cell population, called ‘brain tumor stem cells (BTSC)’. These malignant stem cells proliferate and form the entire tumor mass. Initially, we hypothesized that targeted therapeutic strategies, which exploit molecular differences present within a heterogeneous population of brain tumor cells, will lead to the specific eradication of BTSC without causing toxicity. With excellent support by the Childhood Brain Tumor Foundation, we could perform several lines of experiments and successfully identified a transcription factor, FOXM1, as a critical gene to regulate survival and proliferation of BTSC. We then screened our small molecule libraries, available for the clinical researchers at UCLA Neurosurgery, to identify specific inhibitors for FOXM1. Recently, we were extremely excited with the fact that several compounds, approved by the Food and Drug Administration, selectively inhibit the action of FOXM1 in pediatric brain tumors and their stem cells in culture. We are now in the process of designing pre-clinical and clinical trials for pediatric brain tumors with the identified new chemotherapeutic agents.

Considering the limited effects of the current therapies on malignant brain tumors, multiple parallel or compensatory oncogenic pathways exist to allow tumor stem cells to escape and survive. Thus, it is unlikely that a single agent therapy can cure malignant brain tumors, and multiple molecularly-targeted therapies are crucially required to terminate malignant brain tumor growth. Given that in mind, we will continue to seek revealing the entire key signaling mechanisms underlying BTSC survival and proliferation.

Novel strategies targeting molecular aberrations will eventually offer innovative therapeutic approaches for patients with brain tumors. The findings we have obtained by the grant support by the CBTF and will obtain in the future will serve as a rationale to stratify patients in future clinical trials. Along the path, our mission is to make a concrete impact on future prognoses of pediatric patients with these devastating tumors.

2007

Malignant brain tumors in pediatric patients are devastating, with little hope of cure for most patients, and a high chance of morbidity for those who survive. Recent studies have demonstrated that a kind of stem cell—so-called “cancer stem cells”—exist in malignant brain tumors. In this project, we seek to reveal the mechanism underlying growth of cancer stem cells, and to discover inhibitors of the stem cell growth in order to achieve better prognoses of affected patients.

Our previous study identified that a transcription factor, FoXM1, is highly expressed in brain tumor stem cells, and is required for their growth in culture. These findings suggest that FoXM1 regulates growth of pediatric brain tumors by regulating proliferation of their stem cells. In fact, brain tumor patients with higher expression of FoXM1 have tendency of shorter survival periods. Therefore, we hypothesize that FoXM1 is a potential therapeutic target for pediatric brain tumors. Our project will reveal the function of FoXM1 by utilizing RNA interference to disrupt FoXM1 expression in brain tumor stem cells. We will also utilize our small molecule libraries to identify FoXM1 inhibitors as potential therapeutic compounds for pediatric brain tumors.

PUBLICATION LIST (during the funded period)

1. Phosphoserine phosphatase is expressed in the neural stem cell niche and regulates neural stem and progenitor cell proliferation. Nakano I, Dougherty JD, Kim K, Klement I, Geschwind DH, Kornblum HI. *Stem Cells* 2007 Aug;25(8):1975-84.
2. Maternal embryonic leucine zipper kinase (MELK) is a key regulator of the proliferation of malignant brain tumors, including brain tumor stem cells. Nakano I, Saigusa K, Masterman-Smith M, Horvath S, Watanabe M, Negro A, Paucar AA, Lelievre V, Waschek JA, Lazareff JA, Freije WA, Liau LM, Gilbertson RJ, Cloughesy T, Geschwind DH, Nelson SF, Mischel PS, Tesrskikh A, Kornblum HI. *J Neurosci Res* 2007 Aug 24;86(1):48-60
3. Brain tumor stem cells. **Nakano I**, Kornblum HI. *Pediatr Res*. 2006 Apr;59(4 Pt 2):54R-8R. Review.
4. BMPing Off Glioma Stem Cells. **Nakano I**, Saigusa K, Kornblum HI. *Cancer Cell* 2008 Jan 8;13(1):3-4. Comment.
5. Self-renewal signaling pathways in neural stem cells and brain tumor stem cells. **Nakano I** (*corresponding author*) and Kornblum HI. *Methods in Molecular Biology*. 2007 (*in Press*)

PRESENTATION (selected, during the funded period)

1. Maternal embryonic leucine zipper kinase (MELK) regulates proliferation of brain tumor stem cells. Annual Meeting of American Association of Neurological Surgery, San Francisco, 2006
2. Identification of inhibitors of pediatric brain tumor stem cells. AANS/CNS Section on Pediatric Neurological Surgery, Colorado, 2006
3. Characterization of inhibitors of pediatric brain tumor stem cells. AANS/CNS Section on Pediatric Neurological Surgery, Miami, Oct 2007
4. Stem cells in Pediatric brain tumors. Clinical Neurosurgical Symposia, UCLA 2006
5. Brain tumor stem cells. The 13th annual meeting of the Japan Society of Gene Therapy, Nagoya, 2007
6. Neural stem cells and brain tumor stem cells. Encino-Tarzana Regional Medical Center, Los Angeles, 2007
7. Signaling mechanisms regulating brain tumor stem cell growth. the Annual meeting of the Cell Transplantation Society. Minneapolis, 2007
8. Clinical Implication of Neural Stem Cells and Brain Tumor Stem Cells. Educational Lecture for staff in PICU at UCLA, 2007
9. Luncheon Seminar; Brain Tumor Biology. The 12th Asian Australasian Congress of Neurosurgical Surgeons / World Federation of Neurosurgical Societies, 13th Interim Meeting, Nagoya, 2007

AWARD FOR OUR WORK (during the funded period)

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| 2006 | Journal of Neuro-Oncology Award (in the Annual Meeting of the AANS, San Francisco) |
| 2008 | American Brain Tumor Association Young Investigator Award (in the Annual Meeting of the AANS, Chicago) |