Viral molecular mimicry as a potential immunotherapeutic strategy for glioblastoma multiforme

One of the most challenging scientific problems in brain tumor research is finding a cure for glioblastoma multiforme (GBM). The incidence of primary brain tumors has increased dramatically over the past several decades. More that 18,000 patients are diagnosed in the USA and more than half a million worldwide *[Brandess AA. Semin Oncol. 2003;30 (suppl 19):4-9].* In the pediatric population, primary brain tumors are second in frequency to leukemia and have shown a significant increase in recent years *[Bleyer WA. Childs Nerv Syst. 1999:15:758-763].* Primary brain tumors currently account for about 22% of all pediatric malignancies. About 50% of these are astrocytic gliomas *[Ganigi PM. et. al., Pediatric Neurosurgery. 2005; 41:292-299].* Despite major improvements in therapeutic modalities such as neurosurgery, radiation and chemotherapy, not only have we failed to cure GBM, but the use of these therapies often leads to severe and debilitating side effects.

ETIOLOGY & PATHOPHYSIOLOY

The etiology of GBM is undetermined. GBM is an anaplastic, highly cellular tumor with poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells, nuclear atypia, and anaplasia, endothelial proliferation and pseudo-palisading necrosis. Under the modified WHO classification , GBM is referred to as a grade IV astrocytoma. The predominant signs and symptoms of GBM include a combination of focal neurological deficits due to compression and infiltration of the surrounding brain, vascular compromise, and raised intracranial pressure *[Uddin ABM, et al., http:// www.emedicine.com/NEUO/topic147.htm].* Primary GBM develops de novo from glial cells, typically has a history of < 6 months, and is common in older patients. It demonstrates a high rate of epidermal growth-factor receptor over expression, phosphatase and tensin homologue deleted on chromosome 10 mutations and p16INK4A deletions *[Benjamin R, et al., Cancer J. 2003; 3:82-90].* In contrast, secondary GBM develops in younger patients from a malignant transformation of a previously diagnosed low-grade tumor. Tumor protein 53 and platelet-derived growth-factor and retinoblastoma gene mutation are more common. The improved understanding of the mechanism of the disease has led to advances in the use of existing agents and the development of new target therapies.

CURRENT TREATMENT OF GBM

The median survival duration for patients with GBM is only 9 to 15 months, and the majority of them die within 2 years. Without therapy, patients with GBM uniformly die within 3 months *[Uddin ABM, et. al., http://www.emedicine.com/NEUO/topic147.htm].* Treatment of GBM often fails because the tumors are highly resistant to conventional catatonic chemotherapy and radiotherapy. However, recently gained knowledge in growth-factor receptor signaling pathways has elucidated a new potential therapeutic target.

Novel therapies targeting mechanisms involved in cell cycle, dysregulation, evasion of apoptosis, angiogenesis and escape from immune regulation offer promise for improving the prognosis of GBM patients. So far, over 100 clinical trials of novel targeting therapies are being conducted at the Clinical Center at NIH. Most of these novel agents have proven to be well tolerated but have limited efficacy *[http://www.clinicaltrials.gov].* The main setback with treating GBM is that the therapies have not been associated with any signaling pathway genetic defect; therefore, most of the drug therapies are not specific to GBM.

A MAJOR CHALLENGE IN BIOMEDICAL RESEARCH

Thirty years after the discovery by Milstein and Kohler, monoclonal antibodies have now come of

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age as therapeutics. Nineteen monoclonal antibodies are on the market and/or have received authorization to be used for the treatment of severe disease *[Siberil S. et al. Transfus Clin Biol 2005; 12: 114-22].* The development of hybridoma technology and the advances of monoclonal antibody production have revitalized the concept of cancer cell-target specific "magic bullets" *[Bodey B, et. al., Curr Pharm Des. 2000; 6:261-76].* In addition, the use of proteomics and genomics combined with phage display now allows the rapid selection of antibodies directed against new targets at a high rate. The applications of these technologies, targeting specific antigens for killing GBM, are ideal immunotherapy tools. Our findings of several specific proteins from GBM cross-reactivity with V3 loop antibodies represent a great potential for immunotherapy. Seminal contributions in biomedical sciences often happen when lessons from one field, such as AIDS research, are translated into projects and potential new therapies in other fields, such as cancer.

MOLECULAR MIMICRY STUDIES

We unexpectedly discovered that the anti-HIV-1 gp120 V3 antibodies induced apoptosis in glioblastoma cell lines [***Trujillo*** *et al, J Neurovirology,2000; 6:257; Trujillo et al., unpublished results].* We determined that the antibodies to HIV-1 gp120 V3 loop cross-reacted with normal and malignant human brain proteins, a phenomenon known as molecular mimicry *[**Trujillo** et. al., J Virology, 1993; 67:7711-7715]*. Surprisingly, we found several cross-reacting V3-like epitopes that were exclusive to malignant tumor cells (Figure 1).

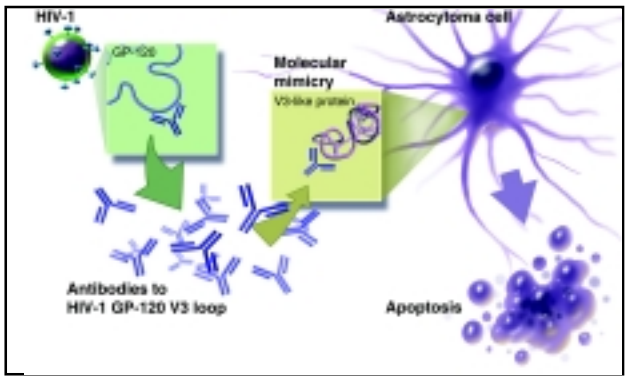

Figure 1. Molecular mimicry and apoptosis of astrocytoma cells. The V3 loop of HIV-1 gp120 shares homology with endogenous proteins from astrocytomas cells. The V3 antibodies induce apoptosis *in vitro* in astrocytoma cells.

If these findings of killing tumor cells by anti-HIV-1 antibodies in the laboratory were to occur "*in vivo*", then we would expect to observe a low incidence of GBM in AIDS individuals. Interestingly, we have observed just that, a low incidence of GBM in AIDS patients (see data below) (Figure 1).

LOW PREVALENCE OF GBM IN AIDS

We previously compared two populations of patients with brain tumors, those with and without AIDS who underwent stereotactic brain biopsy [*Gildenberg PL, Langford L, Kim JH,* ***Trujillo*** *R. Acta Neurochi [Suppl] 1993, 58:68-70*]. Primary CNS lymphomas were the most common tumor found in AIDS patients. In contrast, astrocytomas (mainly GBM) were the most common primary brain tumor in those patients without AIDS. In another cross-sectional epidemiological NeuroAIDS study between the USA and Mexico, we found only a few cases of GBM in a USA population and did not find any cases in a Mexican population [***Trujillo,*** *et al., J AIDS 1995; 8:23-29*]. There seems to be a common pattern of low incidence of astrocytomas in AIDS patients. To further investigate this intriguing question, we reviewed the literature regarding incidence of primary brain tumors in AIDS patients, and up to 2005, only a few cases of GBM have been reported in the AIDS population *[unpublished results*]. The low incidence of GBM in AIDS patients supports our hypothesis that neutralizing HIV-1 antibodies by cross-reacting with tumor antigens due to molecular mimicry may actually prevent the developing GBM in AIDS patients.

The unexpected discovery that the anti-HIV-1 gp120 V3 antibodies induced apoptosis in glioblastoma cell lines represents a new and a distinct direction in finding a cure for malignant brain tumors. The strategy for the employment of antibodies specific to cancer epitopes and the availability of preclinical experimental animal models such as nude mice could lead to rapid development of clinical trials. In *toto*, an innovative approach for the treatment of malignant tumors can be accomplished by using viral molecular mimicry as an immunotherapeutic strategy for tumor cell-directed apoptosis.

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