Stem Cell-Mediated Oncocidal Gene Therapy of Glioblastoma (GBM)

Grant Award Details

Stem Cell-Mediated Oncocidal Gene Therapy of Glioblastoma (GBM)

Grant Type: Disease Team Research I

Grant Number: DR1-01426

Investigator:

Name: Mitchel Berger
Institution: University of California, San Francisco
Type: PI

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Name: Evan Snyder
Institution: Sanford Burnham Prebys Medical Discovery Institute
Type: Co-PI

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Name: Webster Cavenee
Institution: Ludwig Institute for Cancer Research
Type: Co-PI

Disease Focus: Brain Cancer, Cancer, Solid Tumors

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $6,214,914

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Stem Cell-Mediated Oncocidal Gene Therapy of Glioblastoma (GBM)

Public Abstract: Brain tumors (BTs) are incurable, whether they start in the brain or spread there from other sites. Despite advances in surgical, radiation, pharmacologic, and gene therapies, survival with a BT remains dismal. Current therapies are limited by their inability to reach widely disseminated tumor cells that become dispersed within normal brain structures. Interestingly, the therapeutic property that is needed to overcome this major obstacle to effective treatment of BTs matches well with one of the better accepted attributes of neural stem cells (NSCs): an attraction for sites of pathology in the adult brain, including primary & metastatic cancer. If armed with a proper tumor-killing gene, NSCs (whether administered into the brain or into the bloodstream), that are drawn to cancers, will dramatically reduce tumor burden, and will track after even single migrating tumor cells. The NSCs perform this action without themselves becoming tumorigenic or augmenting the pre-existing tumor, and this can be assured by having NSCs express a suicide gene that can be activated and cause NSCs to die. The tumor homing phenomenon of NSCs was first revealed by researchers on this proposed team and, in fact, the central concepts presented here have since been extended to many other kinds of disease. In this proposal, we will use a number of authentic mouse models of primary BTs to pre-clinically test therapeutic NSCs. Human NSCs (hNSCs) will be derived from 3 distinct sources, with each having been proffered as therapeutic, but never having been compared head-to-head in treating tumors. Each of these hNSCs will be modified using two therapeutic genes: TRAIL, which is a protein that specifically kills tumor cells, but does not harm normal cells and tissues, and cytosine deaminase which converts a non-toxic chemical into a toxic chemotherapeutic. We expect our research to identify the best hNSC + therapeutic gene combination to advance for clinical trial in patients with BTs, following our obtaining regulatory approval for using hNSC therapy at the end of this project. Because immunocompatibility of the hNSCs with recipient patients is not a concern in BT therapy, a limited number of hNSC lines can be used for treating all prospective patients. Furthermore, BT treatment does not require long-term NSC survival and can be combined with commonly used BT therapies. Finally, NSCs can be imaged in patients and therefore monitored after administration. Developing this approach for treatment of BT patients offers an ideal setting and opportunity for achieving dramatic results from stem cell therapy, and the results of this project will likely be applicable to the treatment of other cancers.

Statement of Benefit to California:	Brain tumors (BTs) are incurable, whether they start in the brain or spread there from other sites. Despite advances in surgical, radiation, drug, & gene therapies, survival with a BT is extremely short, because current therapies are limited by their inability to reach tumor cells that spread widely to normal brain structures. Interestingly, the therapeutic property that is needed to overcome this major treatment obstacle matches well with one of the better accepted attributes of neural stem cells (NSCs): an attraction for sites of disease in the adult brain, including primary & metastatic cancer. If engineered to be armed with a tumor-killing gene, NSCs (whether administered into the brain or into the bloodstream), that are attracted to cancers, could dramatically reduce patient tumor burden, and track after even single migrating tumor cells, in a manner that has never been achieved. The NSCs would perform this action without themselves causing tumors or increasing growth of the patient's tumor, and this would be assured by engineering the NSCs to self-destruct. The tumor homing phenomenon of NSCs was first revealed by researchers on this proposed team and, in fact, the central concepts presented here have since been extended to many other kinds of disease. In this proposal, we will use a number of authentic mouse models of primary BTs to test therapeutic NSCs before testing them in humans. Human NSCs (hNSCs) will be derived from 3 distinct sources, with each having been proposed as therapeutic, but never having been compared head-to-head in treating cancer. Each of these stem cells will be modified using two different therapeutic genes: TRAIL, a protein that specifically kills tumor cells, but does not harm normal cells and tissues, and cytosine deaminase, which converts a non-toxic chemical into a chemotherapy drug that kills the tumor. We expect our research to identify the best hNSC + therapeutic gene combination to advance for evaluation in clinical trials in patients with intracranial BTs, after we have performed all necessary animal safety testing and submitted a complete plan for review by the US FDA and NIH. Members of this proposed team have experience in bringing cancer therapies to clinical trial, hold the IP surrounding the use of stem cells against cancer, have begun discussions with the FDA and NIH, and have enlisted a GMP facility. Because immune system compatibility between donor and recipient of the hNSCs with the recipient is not a concern in BT therapy, a small number of donors could be used to produce genetically modified hNSCs to treat all prospective patients. Developing this approach for treatment of BTs offers an ideal setting and opportunity for achieving dramatic results from stem cell therapy, and accomplishing substantial improvements in quantity and quality of life for BT patients would no doubt increase California's worldwide visibility in offering the best possible medical care for cancer patients.

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