Recombinant Bispecific Antibody Targeting Cancer Stem Cells for the Therapy of Glioblastoma

Grant Award Details

Recombinant Bispecific Antibody Targeting Cancer Stem Cells for the Therapy of Glioblastoma

Grant Type: Disease Team Therapy Planning I
Grant Number: DR2-05373
Investigator: Name: Albert Wong
Institution: Stanford University
Type: PI

Disease Focus: Brain Cancer, Cancer, Solid Tumors
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Progress Reports

Reporting Period: Year 1
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Grant Application Details

Application Title: Recombinant Bispecific Antibody Targeting Cancer Stem Cells for the Therapy of Glioblastoma
Glioblastoma multiforme is the most prevalent and aggressive type of brain tumor, and devastating to any patient unfortunate enough to receive its diagnosis. As the most populous state in the nation, more Californians are diagnosed with glioblastoma multiforme than any other state. Over the past 20 years, surgery, radiation therapy and chemotherapy have been utilized with frustrating results. Today, even with the most advanced treatments available, survival rates average only 14-15 months.

Our proposed research focuses on a new theory that brain tumor cells are initiated and maintained by a small fraction of cells with stem cell-like properties. This “cancer stem cell” hypothesis states that if this small subset of cancer stem cells could be eliminated then the tumor would cease to grow. Cancer stem cells in glioblastoma have been identified using CD133, a well known marker for isolating normal neural stem cells. The fact that CD133 is present on normal stem cells means that only targeting this molecule would be potentially dangerous. To enhance targeting, we reasoned that a cancer-specific alteration found in glioblastoma could be used as a potential marker for cancer stem cells. EGFRvIII is a specific variant of the normal EGF receptor and is widely found in glioblastoma but is rarely present in normal tissues. We have now shown that tumor cells that express both CD133 and EGFRvIII have the most cancer stem cell properties—more so than cells that have CD133 or EGFRvIII alone. We then developed a “bispecific” antibody that simultaneously recognizes both of these markers and we have shown that this bispecific selectively kills the cancer cells in glioblastoma tumors that express both CD133 and EGFRvIII. However, the bispecific did not kill normal stem cells. These results are very promising and suggest that bispecific can be tested as a therapeutic for glioblastoma.

To move this into patients, we will produce large quantities of the bispecific and perform rigorous tests to ensure that it is uniform and has the required properties. We will also determine that it is safe through a combination of cell based and animal studies. Extensive planning will be made for the correct format for the clinical trial to test this molecule. Once the properties of the bispecific are certified and plans for the clinical trial are finalized, we will submit the drug to the FDA for an Investigational New Drug application. Once approved by the FDA, we can then move forward with testing this compound in glioblastoma patients. We are particularly excited about the bispecific as it could serve as the paradigm for a new class of drugs that specifically target cancer stem cells.
Statement of Benefit to California:

Glioblastoma is a devastating diagnosis. The most common and malignant form of brain cancer, the most aggressive treatments currently available yield an average survival of only 14-15 months. As the most populous state in the nation, more Californians are diagnosed with glioblastoma each year than any other state, with a consequent significant economic toll to the state as well as its emotional toll.

As the leader in cutting edge biomedical research, California through CIRM has recognized the unmet need to provide a roadmap for the translation of stem cell research to clinical applications. Through CIRM there is an unparalleled opportunity to foster clearly-defined discovery that will not only benefit Californians with glioblastomas, but potentially those with many other cancers, and ultimately all Californians, through healthier citizens, increased employment opportunities, and reduced economic burdens.

We have previously shown that two markers of cancer stem cells, CD133 and EGFRvIII, are tightly associated in glioblastoma tumors. We created a recombinant bispecific antibody (BsAb) selectively targeting CD133 and EGFRvIII. This antibody selectively kills glioblastoma tumor cells but not healthy cells. When glioblastoma cells pre-treated with BsAb were injected into mice, tumor formation was significantly reduced, strongly suggesting that targeting of the EGFRvIII/CD133 cancer stem cell population can inhibit glioblastoma formation.

The key objective of our project is to identify efficient and high yield methods for BsAb production, identify an effective dose and route of delivery for the treatment of brain tumors, and evaluate any potential effects on cells/tissues that express CD133. Our goal is to ready the BsAb for investigational new drug-related development.

Californians will benefit from this research project in several significant ways.
1) Most importantly, this research has the promise to dramatically extend the long-term survival rates for Californians with glioblastomas, with potential applications to multiple other human cancers.
2) The research will take place in California with direct benefit to the California economy through the hiring of employees and purchase of supplies and reagents.
3) With successful completion of the proposed project, a clinical trial will be the direct next step, requiring additional employees along with associated expenditures.
4) If the therapeutic BsAb generated is commercialized, profits derived from the production of the BsAbs by CIRM policy will result in improved treatments to insured patients and lower cost treatments to the uninsured, thus ultimately benefiting all Californians.
5) Finally, funding this research will help raise awareness of California’s prominence as a national and international leader in stem cell research with the potential to benefit glioblastoma patients world-wide.

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