Clinical Investigation of a Humanized Anti-CD47 Antibody in Targeting Cancer Stem Cells in Hematologic Malignancies and Solid Tumors

Grant Award Details

Clinical Investigation of a Humanized Anti-CD47 Antibody in Targeting Cancer Stem Cells in Hematologic Malignancies and Solid Tumors

Grant Type: Disease Team Therapy Development III

Grant Number: DR3-06965

Project Objective: Clinical Investigation of a Humanized Anti-CD47 Antibody in Targeting Cancer Stem Cells in Hematologic Malignancies and Solid Tumors. The project objective is to complete two staggered Phase 1 clinical trials, beginning with a solid tumor trial at Stanford. The second trial in AML will be conducted at Oxford in the UK and will be jointly funded by MRC and CIRM.

Investigator:

Name: Irving Weissman
Institution: Stanford University
Type: PI

Name: Ravindra Majeti
Institution: Stanford University
Type: Co-PI

Name: Paresh Vyas
Institution: University of Oxford
Type: Partner-PI

Disease Focus: Blood Cancer, Cancer, Solid Tumors

Collaborative Funder: UK

Human Stem Cell Use: Cancer Stem Cell

Award Value: $6,505,568
Status: Closed

Progress Reports

Reporting Period: Year 1
View Report

Reporting Period: Year 2
View Report

Grant Application Details

Application Title: Clinical Investigation of a Humanized Anti-CD47 Antibody in Targeting Cancer Stem Cells in Hematologic Malignancies and Solid Tumors

Public Abstract: Most normal tissues are maintained by a small number of stem cells that can both self-renew to maintain stem cell numbers, and also give rise to progenitors that make mature cells. We have shown that normal stem cells can accumulate mutations that cause progenitors to self-renew out of control, forming cancer stem cells (CSC). CSC make tumors composed of cancer cells, which are more sensitive to cancer drugs and radiation than the CSC. As a result, some CSC survive therapy, and grow and spread. We sought to find therapies that include all CSC as targets. We found that all cancers and their CSC protect themselves by expressing a ‘don’t eat me’ signal, called CD47, that prevents the innate immune system macrophages from eating and killing them. We have developed a novel therapy (anti-CD47 blocking antibody) that enables macrophages to eliminate both the CSC and the tumors they produce. This anti-CD47 antibody eliminates human cancer stem cells when patient cancers are grown in mice. At the time of funding of this proposal, we will have fulfilled FDA requirements to take this antibody into clinical trials, showing in animal models that the antibody is safe and well-tolerated, and that we can manufacture it to FDA specifications for administration to humans.

Here, we propose the initial clinical investigation of the anti-CD47 antibody with parallel first-in-human Phase I clinical trials in patients with either Acute Myelogenous Leukemia (AML) or separately a diversity of solid tumors, who are no longer candidates for conventional therapies or for whom there are no further standard therapies. The primary objectives of our Phase I clinical trials are to assess the safety and tolerability of anti-CD47 antibody. The trials are designed to determine the maximum tolerated dose and optimal dosing regimen of anti-CD47 antibody given to up to 42 patients with AML and up to 70 patients with solid tumors. While patients will be clinically evaluated for halting of disease progression, such clinical responses are rare in Phase I trials due to the advanced illness and small numbers of patients, and because it is not known how to optimally administer the antibody. Subsequent progression to Phase II clinical trials will involve administration of an optimal dosing regimen to larger numbers of patients. These Phase II trials will be critical for evaluating the ability of anti-CD47 antibody to either delay disease progression or cause clinical responses, including complete remission. In addition to its use as a stand-alone therapy, anti-CD47 antibody has shown promise in preclinical cancer models in combination with approved anti-cancer therapeutics to dramatically eradicate disease. Thus, our future clinical plans include testing anti-CD47 antibody in Phase IIB studies with currently approved cancer therapeutics that produce partial responses. Ultimately, we hope anti-CD47 antibody therapy will provide durable clinical responses in the absence of significant toxicity.
Statement of Benefit to California:

Cancer is a leading cause of death in the US accounting for approximately 30% of all mortalities. For the most part, the relative distribution of cancer types in California resembles that of the entire country. Current treatments for cancer include surgery, chemotherapy, radiation therapy, biological therapy, hormone therapy, or a combination of these interventions (“multimodal therapy”). These treatments target rapidly dividing cells, carcinogenic mutations, and/or tumor-specific proteins. A recent NIH report indicated that among adults, the combined 5-year relative survival rate for all cancers is approximately 68%. While this represents an improvement over the last decade or two, cancer causes significant morbidity and mortality to the general population as a whole.

New insights into the biology of cancer have provided a potential explanation for the challenge of treating cancer. An increasing number of scientific studies suggest that cancer is initiated and maintained by a small number of cancer stem cells that are relatively resistant to current treatment approaches. Cancer stem cells have the unique properties of continuous propagation, and the ability to give rise to all cell types found in that particular cancer. Such cells are proposed to persist in tumors as a distinct population, and because of their increased ability to survive existing anti-cancer therapies, they regenerate the tumor and cause relapse and metastasis. Cancer stem cells and their progeny produce a cell surface ‘invisibility cloak’ called CD47, a ‘don’t eat me signal’ for cells of the native immune system to counterbalance ‘eat me’ signals which appear during cancer development. Our anti-CD47 antibody counters the ‘cloak’, enabling the patient’s natural immune system to eliminate the cancer stem cells and cancer cells. Our preclinical data provide compelling support that anti-CD47 antibody might be a treatment strategy for many different cancer types, including breast, bladder, colon, ovarian, glioblastoma, leiomyosarcoma, squamous cell carcinoma, multiple myeloma, lymphoma, and acute myelogenous leukemia.

Development of specific therapies that target all cancer stem cells is necessary to achieve improved outcomes, especially for sufferers of metastatic disease. We hope our clinical trials proposed in this grant will indicate that anti-CD47 antibody is a safe and highly effective anti-cancer therapy that offers patients in California and throughout the world the possibility of increased survival and even complete cure.

Source URL: https://www.cirm.ca.gov/our-progress/awards/clinical-investigation-humanized-anti-cd47-antibody-targeting-cancer-stem-cells