Development of Therapeutic Antibodies Targeting Human Acute Myeloid Leukemia Stem Cells

Grant Award Details

Development of Therapeutic Antibodies Targeting Human Acute Myeloid Leukemia Stem Cells

Grant Type: Disease Team Research I

Grant Number: DR1-01485

Project Objective: To develop a therapeutic antibody directed against CD47, a cell surface target preferentially expressed on acute myeloid leukemia (AML) stem cells.
CD47 functions as a “don’t eat me” signal by binding to SIRPα on phagocytic macrophages, thereby delivering a dominant inhibitory signal.

Investigator:

Name:	Irving Weissman
Institution:	Stanford University
Type:	PI

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Name:	Beverly Mitchell
Institution:	Stanford University
Type:	Co-PI

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

Disease Focus: Blood Cancer, Cancer

Collaborative Funder: UK

Human Stem Cell Use: Cancer Stem Cell

Cell Line Generation: Cancer Stem Cell

Award Value: $18,759,276

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: NCE Year 5

View Report

Grant Application Details

Application Title: Development of Therapeutic Antibodies Targeting Human Acute Myeloid Leukemia Stem Cells

Public Abstract: Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow that is rapidly fatal within months if untreated. Even with aggressive treatment, including chemotherapy and bone marrow transplantation, five-year overall survival rates range between 30-40%. Evidence indicates that not all cells in this cancer are the same, and that there is a rare population of leukemia stem cells (LSC) that are responsible for maintaining the disease. Thus, in order to cure this cancer, all LSC must be eliminated, while at the same time sparing the normal blood forming stem cells in the bone marrow. We propose to develop therapeutic antibodies directed against surface markers present in much larger amounts on LSC than on the surface of normal blood forming stem cells. We recently identified and validated several such protein markers including CD47, which we determined contributes to leukemia development by blocking the ingestion and removal of leukemia cells by immune system cells called macrophages. In this way, CD47 acts as a "don't eat me" signal on LSC. Moreover, we determined that monoclonal antibodies (mAbs) directed against CD47, able to block its interaction with macrophages, mask the "don't eat me" signal resulting in ingestion and elimination of leukemia in mouse pre-clinical models. We propose a combination of clinical studies, basic research, and pre-clinical development to prepare a therapeutic antibody directed against CD47 and/or other LSC-specific proteins for Initial New Drug (IND) filing with the FDA, and then a Phase I clinical trial to be conducted at {REDACTED} and in the Collaborative Funding Partner country. In collaboration with the pioneering Collaborative Funding Partner country AML Working Group, we will track expression of the LSC proteins in patient samples and correlate with clinical outcomes. This will allow us to identify particular LSC proteins that must be targeted to achieve cure, thereby prioritizing candidate therapeutic antibodies for clinical development. Concurrently, we will conduct basic research and pre-clinical development to prepare these candidates. Basic research during years 1 and 2 will focus on the characterization of anti-CD47 mAb efficacy, investigation of mAb targeting of additional LSC molecules, and determination of efficacy in combinations with anti-CD47. Pre-clinical development during years 1 and 2 will focus on blocking anti-CD47 mAbs, including antibody humanization and large animal model pharmacologic and toxicity studies. Similar studies will be conducted with the most promising antibodies resulting from our basic research. During years 3-4, we will proceed with GMP grade production of the best candidate, followed by efficacy testing in mouse models and large animal models. Finally, in year 4, we will prepare an IND filing with the FDA/MHRA and develop a Phase I clinical trial with this antibody for the treatment of AML. Ultimately, therapeutic antibodies specifically targeting AML LSC offer the possibility of less toxicity with the potential for cure.

Statement of Benefit to California:	Acute myeloid leukemia (AML) is an aggressive malignancy of the bone marrow with nearly 13,000 new diagnoses annually in the US and 2,200 in the Collaborative Funding Partner country. Current standard of care for medically fit patients consists of several cycles of high dose chemotherapy, and often includes allogeneic hematopoietic cell transplantation. Even with these aggressive treatments, which cause significant morbidity and mortality, relapse is common and the five-year overall survival is 30-40%, but <10% in patients with relapsed or refractory disease or in the majority of AML patients who are over age 65. The goal of this research proposal is to prepare therapeutic antibodies directed against AML stem cell-specific antigens for IND filing with the FDA and a Phase I clinical trial. There are several potential benefits of this research for California: (1) most importantly, this research has the potential to revolutionize current clinical practice and provide a targeted therapy for AML that offers the possibility of less toxicity with the potential for cure; (2) this research will directly contribute to the California economy by funding a contract manufacturing organization to generate and produce GMP-grade clinical antibody, by employing several individuals who will be essential for the conduct of these studies, and through the purchase of equipment and reagents from California vendors; (3) additional clinical and economic benefits for California will derive from the potential application of clinical agents developed here to a number of other human cancers and cancer stem cells; (4) our animal models indicate that a significant fraction of patients with fatal AML can be cured, resulting in savings on their clinical care plus their return as productive contributors to the California economy; (5) if our therapeutic antibodies show clinical benefit in AML, they will be commercialized, and under CIRM policy, profits derived from treating insured patients and lower cost therapies for uninsured patients, would enrich the state and the lives of its citizens; (6) finally, this research has the potential to maintain California as the national and world-wide leader in stem cell technology.

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