Genetic Re-programming of Stem Cells to Fight Cancer

Grant Award Details

Genetic Re-programming of Stem Cells to Fight Cancer

Grant Type: Disease Team Therapy Development - Research

Grant Number: DR2A-05309

Project Objective: Goal of this project to develop an autologous stem cell gene therapy for metastatic Melanoma. Paients own blood forming stem cells will be gene modified using a lentiviral vector encoding NYSO-1 tumor antigen. Gene modified HSC when transplanted in the patient will produce NYSO-1 specific T cells in vivo which will target and eliminate melanoma tumor cells positive for NYSO-1. Specif aims of the project includes preclinical development, filing of an IND and completion of a Phase 1 clinical trial.

Investigator:

Name:	Antoni Ribas
Institution:	University of California, Los Angeles
Type:	PI

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Name:	Nicholas Restifo
Institution:	National Cancer Institute
Type:	Partner-PI

Disease Focus: Cancer, Melanoma, Skin cancer, Solid Tumors

Collaborative Funder: NIH

Human Stem Cell Use: Adult Stem Cell

Award Value: $19,875,776

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Genetic Re-programming of Stem Cells to Fight Cancer

Public Abstract:

Science has made great progress in the treatment of certain cancers with targeted and combination therapies, yet prolonged remissions or cures are rare because most cancer therapies only inhibit cell growth and/or reduce such growth but do not stop the cancer.

The study investigators propose to develop an Investigational New Drug (IND) and fully enroll a phase I clinical trial within the grant period to genetically redirect the patient's immune response to specifically attack the cancer starting from hematopoietic (blood) stem cells (HSC) in patients with advanced forms of the aggressive skin cancer malignant melanoma. Evaluation of immune system reconstitution, effectiveness and immune response during treatment will use imaging with Positron Emission Tomography (PET) scans.

The HSC treatment approach has been validated in extensive studies in the laboratory. The investigators of this grant have recently initiated a clinical trial where adult immune cells obtained from blood are genetically modified to become specific killer cells for melanoma. These cells are administered back to patients. The early data from this study is encouraging in terms of the ability to generate these cells, safely administer them to patients leading to beneficial early clinical effects. However, the adult immune cells genetically redirected to attack cancer slowly decrease over time and lose their killer activity, mainly because they do not have the ability to self-renew.

The advantage of the proposed HSC method over adult blood cells is that the genetically modified HSC will continuously generate melanoma-targeted immune killer cells, hopefully providing prolonged protection against the cancer. The IND filing with the FDA will use the modified HSC in advanced stage melanoma patients. By the end of year 4, we will have fully accrued this phase 1 clinical trial and assessed the value of genetic modification of HSCs to provide a stable reconstitution of a cancer-fighting immune system. The therapeutic principles and procedures we develop will be applicable to a wide range of cancers and transferrable to other centers that perform bone marrow and HSC transplants.

The aggressive milestone-driven IND timeline is based on our:
1) Research that led to the selection and development of a blood cell gene for clinical use in collaboration with the leading experts in the field,
2) Wealth of investigator-initiated cell-based clinical research and the Human Gene Medicine Program (largest in the world with 5% of all patients worldwide),
3) Experience filing a combined 15 investigator initiated INDs for research with 157 patients enrolled in phase I and II trials, and
4) Ability to have leveraged significant institutional resources of on-going HSC laboratory and clinical research contributed ~$2M of non-CIRM funds to pursue the proposed research goals, including the resulting clinical trial.

Statement of Benefit to California:

Cancer is the leading cause of death in the US and melanoma incidence is increasing fastest (~69K new cases/year). Treatment of metastatic melanoma is an unmet local and national medical need (~9K deaths/year) striking adults in their prime (20-60 years old). Melanoma is the second greatest cancer cause of lost productive years given its incidence early in life and its high mortality once it metastasizes. The problem is severe in California, with large populations with skin types sensitive to the increased exposure to ultraviolet light. Most frequently seen in young urban Caucasians, melanoma also strikes other ethnicities, i.e., steady increases of acral melanoma in Latinos and African-Americans over the past decades.

Although great progress has been made in the treatment of certain leukemias and lymphomas with targeted and combination therapies, few options exist for the definitive treatment of late stage solid tumors. When cancers like lung, breast, prostate, pancreas, and melanoma metastasize beyond surgical boundaries, prolonged remissions or cures are rare and most cancer therapies only inhibit cell growth and/or reduce such growth but do not stop the cancer.

Our proposal, the filing of an IND and the conduct of a phase 1 clinical trial using genetically modified autologous hematopoietic stem cells (HSC) for the immunotherapy of advanced stage melanoma allowing sustained production of cancer-reactive immune cells, has the potential to address a significant and serious unmet clinical need for the treatment of melanoma and other cancers, increase patient survival and productivity, and decrease cancer-related health care costs.

The advantage of the proposed HSC methodology over our current work with peripheral blood cells is that genetically modified stem cells will continuously generate melanoma-targeted immune cells in the patient's body providing prolonged protection against the cancer. The therapeutic principles and procedures developed here will be applicable to a wide range of cancers. Good Manufacturing Practices (GMP) reagents and clinical protocols developed by our team will be transferable to other centers where bone marrow and peripheral blood stem cell transplantation procedures are done.

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