

Stem Cells for Immune System Regeneration to Fight Cancer

Grant Award Details

Stem Cells for Immune System Regeneration to Fight Cancer

Grant Type: New Faculty II

Grant Number: RN2-00902

Project Objective: The project objective is use gene modified autologous hematopoietic stem cells to reconstitute immune system of the host with chimeric TCR targeting melanoma

Investigator:

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

Disease Focus: Cancer, Melanoma, Solid Tumors

Human Stem Cell Use: Adult Stem Cell

Award Value: \$3,072,000

Status: Closed

Progress Reports

Reporting Period: Year 1

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Grant Application Details

Application Title: Stem Cells for Immune System Regeneration to Fight Cancer

Public Abstract: This proposal will define the biology of stem cell engineering to produce a cancer-fighting immune system. The immune system protects our body against most outside threats. However, it frequently fails to protect us from cancer. The T cell receptor (or TCR), a complex protein on the surface of an immune cell (or lymphocyte), allows to specifically recognize cancer cells. The TCR functions like a steering wheel for lymphocytes, allowing them to travel around the body and specifically find and attack cancer cells. The goal of this research is to put TCR genes into stem cells to generate a renewable source of cancer-fighting lymphocytes. The studies in mice provide compelling evidence that inserting TCR genes into stem cells has several advantages for the progeny lymphocytes, allowing them to better fight cancer. The next step is to bring this approach to patients with cancer. The main reason is that the TCR genes inserted into stem cells allow the generation of a larger army of TCR re-directed cancer-fighting killer lymphocytes. I have dedicated most of my prior work to make the transition from studies in mice to the bedside. I have gained the expertise to conduct clinical trials using cells as targeted drugs from patients. This experience has allowed me to design and start working on the clinical trials that will test the concept of inserting TCR genes into progenitors of lymphocytes and give them to patients. With my collaborators at other institutions, we have raised the adequate resources from private foundations and the NIH to initiate clinical trials inserting TCR genes into lymphocytes. I request additional funds from CIRM to allow me to extract the most information from the clinical trials and then help take them one step further by ultimately testing the use of hematopoietic stem cells (HSC) and induced pluripotent cells (iPS) to engineer a cancer-fighting immune system. There are several challenges that need to be addressed, including what is the best approach to generate both immediate and long-term cancer fighting cells, what are the optimal stem cells to target, and how they should be manipulated and given to patients in the clinic. The study of samples obtained from patients participating in pilot clinical trials will provide information how to design new clinical trials using the method of inserting the cancer-specific TCR genes into stem cells. The experience of regenerating a cancer-fighting immune system in humans could then be applied to multiple cancer types and to infectious diseases that currently lack good treatment options.

Statement of Benefit to California: Preclinical studies have validated the concept that the immune system can be harnessed to fight cancer. However, clinical testing has failed short of expectations. I propose to genetically program the immune system starting from stem cells with the hope of advancing cancer immunotherapy. Malignant melanoma will be the cancer for the initial testing of this approach. Melanoma has a track record of being "immune-sensitive" and there are well-defined antigens against which the immune system can be targeted. Melanoma is the cancer with the fastest rising incidence in the U.S. This disease impacts heavily in our society, since it strikes adults at the prime years of life (30-60 years old). In fact, melanoma is the second cancer cause of lost of productive years given its incidence early in life and its high mortality once it becomes metastatic. The problem is particularly worrisome in areas of the world like California, with large populations of persons originally from other latitudes with much lower sun exposure and with skin types unable to handle the increased exposure to ultraviolet (UV) light in California. Although most frequent in young urban Caucasians, melanoma also strikes other ethnicities. The incidence of acral melanoma (non-UV light induced melanoma that develops in the palms and soles) has also steadily increased in Hispanics and Blacks over the past decades. Early melanoma can be cured with surgery. Therefore, programs aimed at early detection have the highest impact in this disease. Once it becomes metastatic, melanoma has no curative standard therapy. Despite this grim outlook, it has been long known that occasional patients participating in experimental immunotherapy protocols have long remissions and are seemingly cured. This proposal aims at incorporating the most current knowledge arising from preclinical research and prior clinical experimentation of immunotherapy strategies to engineer the immune system genetically to better fight metastatic melanoma. Bringing new science from the laboratory to the bedside requires well-designed, well-organized and informative clinical trials. It is not enough to show some responses, we need to understand how they develop and why some patients respond and other do not. Therefore, the analysis of stem cell-based immune system engineering within clinical trials proposed herein requires thorough analysis of patient-derived samples to inform the follow-up clinical testing. Information resulting from the genetic engineering of the immune system in patients with melanoma will help develop studies to direct the immune system to fight other cancers and infectious diseases like HIV. Once optimized, I envision the ability to clone T cell receptor (TCR) genes specific for tumor or infectious disease antigens expressed by different cancers or infectious agents, and use these TCRs to genetically program the patient's immune system to attack them.

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