Dual targeting of tyrosine kinase and BCL6 signaling for leukemia stem cell eradication

Grant Award Details

Dual targeting of tyrosine kinase and BCL6 signaling for leukemia stem cell eradication

Grant Type: Early Translational II

Grant Number: TR2-01816-B

Project Objective: The main objective of this project is to develop an improved lead class of second generation BCL6 lateral groove inhibitors and validate their efficacy in selective eradication of leukemia stem cells in pre-clinical in vivo models.

Investigator:

Name:	Markus Muschen
Institution:	University of California, San Francisco
Type:	PI

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Name:	Andreas Hochhaus
Institution:	University of Jena
Type:	Partner-PI

Disease Focus: Blood Cancer, Cancer

Collaborative Funder: Germany

Human Stem Cell Use: Cancer Stem Cell

Cell Line Generation: Adult Stem Cell, Cancer Stem Cell

Award Value: $2,756,536

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Dual targeting of tyrosine kinase and BCL6 signaling for leukemia stem cell eradication

Public Abstract: Leukemia is the most frequent form of cancer in children and teenagers, but is also common in adults. Chemotherapy has vastly improved the outcome of leukemia over the past four decades. However, many patients still die because of recurrence of the disease and development of drug-resistance in leukemia cells.
In preliminary studies for this proposal we discovered that in most if not all leukemia subtypes, the malignant cells can switch between an “proliferation phase” and a “quiescence phase”. The “proliferation phase” is often driven by oncogenic tyrosine kinases (e. g. FLT3, JAK2, PDGFR, BCR-ABL1, SRC kinases) and is characterized by vigorous proliferation of leukemia cells. In this phase, leukemia cells not only rapidly divide, they are also highly susceptible to undergo programmed cell death and to age prematurely. In contrast, leukemia cells in “quiescence phase” divide only rarely. At the same time, however, leukemia cells in "quiescence phase" are highly drug-resistant. These cells are also called 'leukemia stem cells' because they exhibit a high degree of self-renewal capacity and hence, the ability to initiate leukemia. We discovered that the BCL6 factor is required to maintain leukemia stem cells in this well-protected safe haven. Our findings demonstrate that the "quiescence phase" is strictly dependent on BCL6, which allows them to evade cell death during chemotherapy treatment. Once chemotherapy treatment has ceased, persisting leukemia stem cells give rise to leukemia clones that reenter "proliferation phase" and hence initiate recurrence of the disease. Pharmacological inhibition of BCL6 using inhibitory peptides or blocking molecules leads to selective loss of leukemia stem cells, which can no longer persist in a "quiescence phase".
In this proposal, we test a novel therapeutic concept eradicate leukemia stem cells: We propose that dual targeting of oncogenic tyrosine kinases (“proliferation”) and BCL6 (“quiescence”) represents a powerful strategy to eradicate drug-resistant leukemia stem cells and prevent the acquisition of drug-resistance and recurrence of the disease. Targeting of BCL6-dependent leukemia stem cells may reduce the risk of leukemia relapse and may limit the duration of tyrosine kinase inhibitor treatment in some leukemias, which is currently life-long.

Statement of Benefit to California:	Leukemia represents the most frequent malignancy in children and teenagers and is common in adults as well. Over the past four decades, the development of therapeutic options has greatly improved the prognosis of patients with leukemia reaching 5 year disease-free survival rates of ~70% for children and ~45% for adults. Despite its relatively favorable overall prognosis, leukemia remains one of the leading causes of person-years of life lost in the US (362,000 years in 2006; National Center of Health Statistics), which is attributed to the high incidence of leukemia in children. In 2008, the California Cancer Registry expected 3,655 patients with newly diagnosed leukemia and at total of 2,185 death resulting from fatal leukemia. In addition, ~23,300 Californians lived with leukemia in 2008, which highlights that leukemia remains a frequent and life-threatening disease in the State of California despite substantial clinical progress. Here we propose the development of a fundamentally novel treatment approach for leukemia that is directed at leukemia stem cells. While current treatment approaches effectively diminish the bulk of proliferating leukemia cells, they fail to eradicate the rare leukemia stem cells, which give rise to drug-resistance and recurrence of the disease. We propose a dual targeting approach which combines targeted therapy of the leukemia-causing oncogene and the newly discovered leukemia stem cell survival factor BCL6. The power of this new therapy approach will be tested in clinical trials to be started in the State of California.
