Award ID:
RP160693

Project Title:
Acute Myeloid Leukemia in the Immunosuppressed Microenvironment

Award Mechanism:
Multi-Investigator Research Awards (Version 2)

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Acute myeloid leukemias (AML) are malignant diseases of the bone marrow that rapidly lead to death if left untreated. These leukemias originate in very primitive stem cells in the bone marrow and prevent the development of normal blood cells, including infection-fighting white cells, oxygen-carrying red cells and platelets that prevent bleeding. Prevention is not currently possible and unlike solid tumors the disease is systemic at diagnosis preventing “early diagnosis.” Importantly the incidence is increasing with age, which explains the increase in patients in an aging population. Since 1976 the treatment of AML has consisted of the combined usage of two drugs (ARA-C and DNR) which puts a significant number of patients into complete remissions; however the vast majority of patients relapses and succumbs to their disease. Recently DNA analysis of AMLs has identified a large number of mutations (over 250) with most patients having over 10 mutations. Many drugs are under development to target these genomic abnormalities but given the complexity and heterogeneity of these abnormalities, it may take a very long time to be successful in targeting them all.

Evolving research has identified promising opportunities to not only control but to eliminate AML and this multi-investigator research grant has brought together a very experienced group of physician-scientists to take full advantage of these new discoveries. Leukemic cells, in real life, do not live in plastic dishes, but in the complex microenvironment of the bone marrow where they originate. Importantly, leukemic cells in circulation are very sensitive to chemotherapy and can almost always be eliminated, while bone marrow resident leukemic cells can survive and lead to recurrence of the disease. This suggests that the bone marrow exerts a major protection that prevents elimination of leukemic cells from their bone marrow sanctuaries. New findings by our group indicate that the bone marrow microenvironment in AML is highly deprived of oxygen (hypoxia). This is surprising given the good blood supply that is found in the marrow. We have now identified a reason for this lack of oxygen as a metabolic abnormality (OxPhos), where leukemic cells derive their energy by consuming the available oxygen. Hypoxia is known in solid tumors to be associated with resistance to chemotherapy. In collaboration with the Institute for Applied Cancer Science (IACS) at MD Anderson we have developed a specific inhibitor of this process. The drug shows excellent anti-leukemia activity and is also able, at least in part, to reverse the hypoxia. We here propose to test this potentially game-changing new anti-cancer drug in patients with AML (Project 1 Aim 1).

Hypoxia in the marrow has many consequences that help in the survival of leukemic cells. One is the up-regulation of a mechanism that anchors the leukemic cells in the protective bone marrow, through a receptor termed CXCR4. Patients with high expression of CXCR4 have a most unfavorable prognosis. We have used CXCR4-targeted drugs in the past and have seen that they can kill leukemic cells and make them more sensitive to other anti-leukemia drugs. Here we propose to use two of the most effective, latest-generation CXCR4 inhibitors in combination with chemotherapy in one trial, and in combination with a mutation-inhibitor in a second trial. The specific mutation, FLT3-ITD, conveys an adverse prognosis in AML. It also has the highest expression of CXCR4, and in a previous trial targeting CXCR4 and FLT-ITD we achieved excellent responses and WE wish to further improve on this concept (Project 1 Aim 3). In addition we have developed an imaging system where we can visualize leukemic cells in their natural bone marrow environment in mice. This system will allow us to further characterize the specialized bone marrow niches that protect leukemia stem cells and we expect that this research will help us to further develop our treatment strategy (Project 1 Aim 2).

The immune system has long been the focus of cancer research. However, until recently only limited progress had been made exploiting the ability of immune cells to fight cancer. The best example of immunotherapy is bone marrow transplantation where immune cells from a donor attack the leukemia cells. Two kinds of cells have been found responsible for these effect, T-lymphocytes and natural killer (NK) cells. Project 2 focuses on NK cells obtained from cord blood. Investigators of Project 2 have shown that NK cell function is suppressed by AML cells. They are proposing to expand NK cells obtained from cord blood, which is routinely used for stem cell transplantation, and to infuse these cells into patients with AML (Project 2 Aim 1). Furthermore they are targeting leukemia stem cells with off-the-shelf, gene-modified NK cells using a CD123-directed chimeric antigen receptor (CAR). CD123 is the best investigated marker of leukemic stem cells and preclinical studies are highly promising (Project 2 Aim 2). Another factor that suppresses the immune cells is called TGFb, which is produced by leukemic cells. Inhibition of TGFb has greatly enhanced the activity of NK cells and Aim 3 will exploit this finding to optimize the activity of NK cells against leukemias.

An alternative and complimentary approach to counteract the hypoxic and immunosuppressive bone marrow microenvironment explores the ability of T-lymphocytes to kills leukemia targets. Project 3 investigators have developed a novel T-cell termed “bispecific T-cell engagers” (ENG-T cells) which redirect bystander T-cells to leukemias. These CD123-ENG-T cells have demonstrated potent anti-leukemia activity (Project 3 Aim 1 & 2). We now wish to evaluate these cells in humans. In addition Project 3 will investigate the combined effects of CXCR4 inhibition and ENG-T cells, in collaboration with Project 1, and combined effects of ENG-T and ENG-NK cells (Project 3 Aim 3 & 4).

Taken together the novel concepts proposed in this multi-investigator grant application attack leukemias in ways that are not only innovative but also exploit basic mechanisms of leukemia cell protection that have only recently been recognized.

The projects are supported by 3 outstanding scientific cores and one administrative core. Core 1 will provide leukemia samples for our studies and is based on the well-established leukemia bank that these investigators have built up over 25 years. The Core also provides analysis gene expression molecules (both protein and RNA) and is able knock-out specific genes with most effective technology known (CRISPR). Core 2 is providing cell analysis at multiple levels from imaging in laser microscopes to sorting of individual cells and stem cells at a rate of over 50,000 cells per second (FACS) to the analysis of up to 40 proteins per cell/stem cell (CyTOF). These technologies are cutting edge and allow unprecedented mapping of cell signaling pathways which determine the life/death decisions in leukemia cells. Core 3 then provides highly innovative biostatistics and bioinformatics support to analyze the effects of our proposed novel treatment on leukemia cells and stem cells and optimally design our clinical trials. Finally the Administrative Core integrates all projects and scientific cores, provides oversight and reports and importantly organizes internal and external advisory boards that will critique and help in the development of the proposed projects.

We strongly believe that our MIRA Program, as proposed here, will have major impact on

the lives of our AML patients. Each of the projects is highly innovative, very well grounded in latest discoveries in cell biology and immunology and driven by highly experienced investigators who are all seeing patients with AML on a daily basis. Funding for this program would bring us closer to curing AML.