Combinatorial Chemistry Approaches to Develop LIgands against Leukemia Stem Cells

Grant Award Details

Combinatorial Chemistry Approaches to Develop LIgands against Leukemia Stem Cells

Grant Type: New Faculty I

Grant Number: RN1-00561

Project Objective: The objective of this project is to make AML leukemia stem cell (LSC) targeted nanomicelles carrying the chemotherapeutic daunorubicin, and to demonstrate that these kill LSC in vitro and in vivo.

Investigator:

Name:	Chong-Xian Pan
Institution:	University of California, Davis
Type:	PI

Disease Focus: Blood Cancer, Cancer

Human Stem Cell Use: Adult Stem Cell, Cancer Stem Cell

Cell Line Generation: Cancer Stem Cell

Award Value: $2,386,409

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Combinatorial Chemistry Approaches to Develop LIgands against Leukemia Stem Cells

Public Abstract: Various cells and organs in the human body originate from a small group of primitive cells called stem cells. Human cancer cells were also recently found to arise from a group of special stem cells, called cancer stem cells (CSCs). At present, cancer that has spread throughout the body (metastasized) is difficult to treat, and survival rates are low. One major reason for therapeutic failure is that CSCs are relatively resistant to current cancer treatments. Although most mature cancer cells are killed by treatment, resistant CSCs will survive to regenerate additional cancer cells and cause a recurrence of cancer. As opposed to other human stem cells, CSCs have their own unique molecules on their cell surface. This project aims to develop agents that specifically target the unique cell surface molecules of CSCs. These agents will have the potential to eradicate cancer from the very root, i.e., from the stem cells (CSCs) that produce mature cancer cells. In this project, we will develop agents that specifically target leukemia stem cells to determine the feasibility of our approach. Leukemia is the fourth most common cause of cancer death in males and the fifth in females. If our approach is successful, we can use the same approach for other cancer types. To develop these specific agents, we will screen a library of billions of molecules to identify those that specifically target the unique cell surface molecules of leukemia stem cells (LSCs). After we identify these specific molecules, we will optimize their structure to increase their specific binding to LSCs. Specific binding to LSCs is crucial, as the optimized molecules will be able to uniquely kill LSCs and spare normal blood cells.

Many leukemia patients need stem cell transplantation during treatment. There are two approaches to harvesting stem cells for transplantation: those harvested from patients themselves and those harvested from healthy donors. Stem cells harvested from healthy donors need to genetically match patients' cells. Otherwise, these transplanted cells from the donor recognize the recipient's (host or patient) cells as non-self cells and attack these cells. This response leads to a serious disease called graft-versus-host disease (GVHD). It is often difficult to find matched donors. Stem cells harvested from patients are usually not used for the treatment of acute leukemia because they are contaminated with LSCs that will lead to recurrence of leukemia after transplantation. If this project is successful, the targeting agents developed in this project can be used to eliminate the contaminating LSCs and decrease the leukemia recurrence after transplantation.

Statement of Benefit to California:

Acute leukemia is the sixth most common cause of cancer death in males and females in California. The outcome for acute leukemia is poor and over 70% of patients will die from this disease. This project aims to develop therapeutic agents that specifically target leukemia stem cells and therefore eradicate leukemia from its root. These agents can also be used for stem cell transplantation. Many leukemia patients need stem cell transplantation during treatment. There are two approaches to harvesting stem cells for transplantation: those harvested from patients themselves and those harvested from healthy donors. Stem cells harvested from healthy donors need to genetically match patients' cells. Otherwise, these transplanted cells from the donor recognize the recipient's (host or patient) cells as non-self cells and attack these cells. This response leads to a serious disease called graft-versus-host disease (GVHD). It is often difficult to find matched donors. This is especially true in California because of the genetically diversified population. Stem cells harvested from patients are usually not used because they are contaminated with leukemia stem cells that will lead to recurrence of leukemia after transplantation. If this project is successful, the targeting agents developed in this project can be used to eliminate the contaminated leukemia cells and decrease the likelihood of leukemia recurrence after transplantation.

The ligands developed in this project can be used for targeted therapy for leukemia. Since no such ligands have been identified so far that specifically target leukemia stem cells, these ligands can be patented and eventually commercialized. This may have huge financial benefits to California. If this project is successful, the same approach can be used to treat other cancers and for the development of more commercialized drugs.

If this grant is funded, it will secure my career as a physician-scientist in stem cell and cancer research. The physician-scientist is a diminishing breed in that it is difficult for physicians to do research while meeting the huge demands of the clinic. However, there is a huge gap between basic research and clinical applications. This gap is in part traced to the fact that it is difficult to find researchers who know and can integrate clinical needs with basic research. I consider myself a promising physician-scientist who has received extensive, rigorous and systematic training in medical science and basic research ([REDACTED]). If this grant is funded, I will not only carry out this important research, but this will also give me protected time for this research.
