

## News from the Field

- ◆ The Children's Oncology Group has developed a new chemotherapy regimen for patients with pediatric Hodgkin lymphoma. According to the online first edition article published in *Blood*, the treatment involves a combination of six drugs, known as ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide). A total of 216 patients younger than 22 years were treated with the new chemotherapy. According to the article, the five-year event-free survival was approximately 84 percent and the five-year overall survival was approximately 95 percent. SOURCE: *Blood*
- ◆ According to a recent article published online in the *Journal of Clinical Oncology*, bendamustine was significantly more effective than chlorambucil as first-line therapy in patients with advanced chronic lymphocytic leukemia (CLL). A total of 319 patients were enrolled in this multi-center, phase III trial. The complete or partial responses for the bendamustine-treated patients and the chlorambucil-treated patients was 68% and 31% respectively. Researchers also indicated that median progression-free survival was 21.6 months with bendamustine and 8.3 months with chlorambucil. SOURCE: *Journal of Clinical Oncology*
- ◆ Researchers from the United Kingdom have found allogeneic stem cell transplantation to be effective for angioimmunoblastic T-cell lymphoma (AITL) patients. According to the article published in the *Journal of Clinical Oncology*, of the 45 patients that were analyzed, 25 patients underwent a myeloablative allogeneic stem cell transplant and 20 patients underwent a reduced-intensive allogeneic stem cell transplant. Researchers indicated that progression free survival and overall survival were 62 percent and 53 percent at 1 year and 66 percent and 64 percent at 3 years, respectively. SOURCE: *Journal of Clinical Oncology*
- ◆ Scientific investigators published a manuscript in the *Journal of Clinical Oncology* indicating that a specific dosage of temsirolimus significantly improves progression free survival and objective response rate when compared with investigator's choice of therapy in relapsed or refractory mantle

cell lymphoma patients (MCL). The multi-center, phase III clinical trial enrolled 162 patients with relapsed or refractory MCL. Patients received one of two temsirolimus regimens: 175 mg weekly for 3 weeks followed by either 75 mg or 25 mg weekly, or investigator's choice of therapy from approved options. The patients receiving temsirolimus 175/75-mg had significantly longer progression free survival (4.8 months) compared with investigator's choice of therapy (1.9 months). The objective response rate was also significantly higher in the 175/75-mg group (22 percent) compared with the investigator's choice group (2 percent). SOURCE: *Journal of Clinical Oncology*

- ◆ According to results of a phase I/II clinical trial published in the *Journal of Clinical Oncology*, velvuzumab appears safe and active in relapsed/refractory B-cell non-Hodgkin lymphoma patients. Eighty-two patients, who received one to nine prior treatments, were enrolled in the study to assess the safety and effectiveness of velvuzumab. For the 55 follicular lymphoma patients enrolled in the trial, the objective response rate (OR) was 44 percent and the complete response rate (CR/CRU) was 27 percent. The OR was 83 percent and the CR/CRU was 33 percent for the six marginal zone lymphoma patients. For the seven diffuse large B-cell lymphoma patients, 43 percent achieved partial responses. SOURCE: *Journal of Clinical Oncology*.

## ATTENTION ALL LYMPHOMA RESEARCHERS!

**LRF will be announcing additional grant opportunities for scientific investigators this Fall.**

**For more details, please visit:**

**[www.lymphoma.org/research/grants](http://www.lymphoma.org/research/grants)**

**For more information, please call:**

**212-349-2910**

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**Thank You!**

# RESEARCH REPORT

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A Report from the Lymphoma Research Foundation

## Introduction

Research makes advances in lymphoma treatment possible. Through research, clinicians and scientists are constantly learning more about cancer and its development. For this reason, the Lymphoma Research Foundation (LRF) continually strives to find the world's best scientific talent and fund the most cutting-edge research.

To accomplish this goal, LRF awards grants to promising scientific investigators conducting research on various areas of lymphoma. Over the years, LRF has awarded a total of 265 grants. These grants have been given to both junior and senior investigators and have supported projects ranging from biological to clinical studies. This year, LRF is providing one Clinical Investigator Career Development Award and two Chronic Lymphocytic Leukemia (CLL) Clinical Study awards.

The first portion of this Report contains project descriptions of the three grantees that were selected: Kai Fu, MD, PhD, David Frank, MD, PhD and Thomas Kipps, MD, PhD. This is followed by *News from the Field* which contains some of the latest research findings and treatment advances to emerge in the field of lymphoma.

## A Closer Look at LRF's Latest Grantees

Recently, the Lymphoma Research Foundation (LRF) received numerous applications for several of its research grant programs, including its Clinical Investigator Career Development Award and Chronic Lymphocytic Leukemia (CLL) Clinical Study Award.

All of the grant applications were reviewed by members of LRF's Scientific Advisory Board (SAB), a voluntary group of 45 renowned lymphoma experts. The research projects and applicants showing the greatest potential were recommended to LRF's Board of Directors for funding.

This year, LRF is excited to be awarding one Clinical Investigator Career Development Award and two CLL Clinical Study Awards to three pioneers in the field of lymphoma research: Kai Fu, MD, PhD, David Frank, MD, PhD and Thomas Kipps, MD, PhD.

The following sections contain in-depth interviews with these newest grantees. LRF will continue to update you on the promising contributions these talented investigators will be making to the field of lymphoma in future issues of the *Research Report*.

## CLINICAL INVESTIGATOR CAREER DEVELOPMENT AWARD

The Lymphoma Research Foundation (LRF) provides Clinical Investigator Career Development Awards (CDAs) to researchers that are interested in developing new therapeutics and diagnostic tools for lymphoma. These three-year grants are used to prepare clinicians to design and administer clinical studies. Since 2002, LRF has awarded 12 CDAs.

### Kai Fu, MD, PhD

University of Nebraska Medical Center, Omaha, NE

Dr. Kai Fu received the 2009 Millennium Pharmaceuticals, Inc./Lymphoma Research Foundation Clinical Investigator Career Development Award to determine the role of the miR-17~92 cluster in the development of MCL.

Dr. Kai Fu is an Associate Professor and Staff Hematopathologist in the Department of Pathology and Microbiology at the University of Nebraska Medical Center. He earned a medical degree from Tianjin Medical University and a PhD in Biochemistry and Molecular Biology from the University of Kansas Medical Center, Kansas City, Kansas.

Mantle cell lymphoma (MCL) is an aggressive lym-

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## LYMPHOMA RESEARCH FOUNDATION

The Lymphoma Research Foundation (LRF) is the nation's largest lymphoma-focused voluntary health organization devoted exclusively to funding lymphoma research and providing patients and health care professionals with critical information on the disease. LRF's mission is to eradicate lymphoma and serve those touched by this disease.

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phoma characterized by a specific chromosomal translocation—a genetic event that occurs when a small piece of one chromosome switches places with a small piece of another chromosome. However, scientists have recently discovered that the translocation alone may not result in the development of MCL and that secondary alterations may play a vital role.

According to Fu, one of the most frequently occurring alterations targets the miR-17~92 cluster, a group of seven microRNAs (short pieces of genetic material that regulate gene expression) which are crucial for B-cell development. Previous studies have shown that higher expression of this cluster is related to poorer survival in patients with MCL.



As a result, Fu and his colleagues set out to discover the molecular mechanisms behind this negative association. “We found that higher miR-17~92 expression induces abnormal activation of a pathway in tumor cells that causes the tumor cells to become more resistant to standard chemotherapy,” says Fu.

With the funding he received, Fu will further examine the cluster’s role in the development of MCL as well as the feasibility of using the miR-17~92 cluster as a therapeutic target.

“We will conduct a pre-clinical study to determine whether suppression of miR-17~92 will improve the effect of chemotherapy, thus providing a novel approach to treat patients with this deadly disease in the future. Results from these studies will not only further our knowledge of the biology of MCL, but also promise to provide proof-of-principle data for targeting miR-17~92 in future lymphoma therapy,” says Fu.

The Millennium Pharmaceuticals, Inc./Lymphoma Research Foundation Clinical Investigator Career Development Award is supported by an independent grant from Millennium Pharmaceuticals, Inc. (Millennium). Millennium neither controlled nor influenced the nomination or selection of any award recipient.

## CLL CLINICAL STUDY AWARD

In 2006, LRF started an initiative to develop novel therapeutic strategies for the treatment of chronic lymphocytic leukemia (CLL). The following year, LRF awarded

two, three-year grants to established CLL researchers in the field. As a result, LRF and its SAB decided to develop a CLL Committee for Clinical Trials composed of basic laboratory and clinical research scientists focusing their efforts on CLL. The central charge of the Committee is to foster translational research and inter-institutional collaboration in CLL by promoting, reviewing and awarding grants.

The Committee, currently made up of 11 individuals, recently developed a request-for-proposals focused on translational or clinical studies using novel agents alone or in combination with existing therapies as part of Phase I and Phase II clinical trials.

After an extensive review process, two investigators were awarded a two-year LRF CLL Clinical Study Award.

### David Frank, MD, PhD

Dana-Farber Cancer Institute, Boston, MA

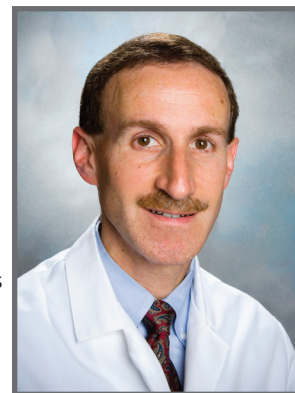
*Dr. David Frank received a CLL Clinical Study Award to perform a Phase I/II clinical trial of pyrimethamine.*

Dr. David Frank, currently an Associate Professor of Medicine in the Department of Medical Oncology at Dana-Farber Cancer Institute and Harvard Medical School, started his research career at Yale University where he earned a combined MD/PhD degree. After finishing an Internal Medicine Residency at Yale-New Haven Hospital, he went on to complete a Medical Oncology Fellowship and a Molecular Genetics Fellowship from Dana-Farber Cancer Institute and Harvard Medical School respectively.

As an oncologist for the past 15 years, Frank has focused his clinical interest on hematology and concentrated his laboratory research on molecular abnormalities of lymphoma, particularly CLL.

In 2007, Frank received a three-year grant from the Lymphoma Research Foundation (LRF) to study STAT1, a cellular protein that controls genes responsible for regulating cell survival. Frank discovered that activating STAT1 caused the death of CLL cells. Therefore, he began identifying and testing several drugs capable of enhancing the activity of STAT1 in animal models.

During his investigation, Frank uncovered evi-



dence suggesting that another cellular protein may play a role in CLL development. “In research we have conducted over the last ten years, we have found that STAT3 is activated inappropriately in essentially every patient with CLL, and may contribute directly to the pathogenesis of this cancer,” says Frank.

As a result of this intriguing discovery, Frank will now be receiving a two-year CLL Clinical Studies Award from LRF to study STAT3.

According to Frank, STAT3 is critical for tumor cell survival. However, it is not a critical element for normal cells. Therefore, STAT3 may be a potentially effective target for the treatment of CLL.

To date, Frank has identified a drug called pyrimethamine which effectively inhibits STAT3 and is safe in humans. With the funding he received from LRF, Frank intends to perform a Phase I/II clinical trial of pyrimethamine in relapsed CLL patients.

“The primary objective of the Phase I study will be to determine the maximal tolerated dose and recommended Phase II dose of pyrimethamine in relapsed CLL patients. Once that dose is identified, the Phase II study will begin. The primary objective of the Phase II study will be to determine the objective response rate of pyrimethamine in relapsed CLL patients,” says Frank.

He went on to state, “This study represents the first proof-of-principle evaluation of a molecular targeted therapy for CLL, and will inform the use of STAT3 inhibitors for the treatment of cancer. At the conclusion of the funding period, we plan to be in a position to critically evaluate and optimize this form of rational molecular therapy for patients with CLL.”

### Thomas Kipps, MD, PhD

University of California, San Diego, LaJolla, CA

**Dr. Thomas Kipps received a CLL Clinical Study Award to test a novel chemo-sensitization strategy in a Phase I clinical trial.**

Dr. Thomas Kipps is currently a Professor of Medicine at the University of California, San Diego (UCSD) and the Deputy Director of Research at the UCSD Cancer Center. He first became interested in research as an undergraduate at Columbia University where he earned a BA in Biochemistry. He then went on to earn a medical degree and a PhD in Immunology from Harvard University.

A major problem facing many CLL patients is the development of chemotherapy resistance. According to Kipps, many of these chemotherapy resistant CLL patients often have a genetic abnormality in chromo-

some 17. This abnormality is often associated with a lack of p53, a molecule that causes cell death when activated by standard chemotherapeutic agents.

“Patients with CLL cells that lack functional p53 will not respond to standard chemotherapy and typically have a poor prognosis and survival,” says Kipps.

In previous laboratory studies, Kipps and his colleagues have discovered that drug-resistant CLL cells can be made sensitive to chemotherapy by using a specific technique called gene-immune therapy. Kipps found that CLL cells lacking p53 can be genetically modified in the laboratory and made more sensitive to certain chemotherapy drugs by circumventing p53 and activating p73, a molecule similar to p53 that also causes cell death when activated by certain chemotherapeutic agents, such as fludarabine.

Additionally, Kipps discovered that these genetically modified CLL cells have the ability to make bystander CLL cells sensitive to chemotherapies that ordinarily require p53.

With funding he received from the Lymphoma Research Foundation, Kipps has initiated studies in cells from patients enrolled in a phase I clinical trial in which patients with refractory disease, or CLL cells with defective p53, receive infusions of their own genetically modified CLL cells. After three such infusions, the patients receive chemo-immunotherapy (fludarabine, cyclophosphamide and rituximab or FCR).

To date, the clinical trial, led by Januario Castro, MD (Assistant Clinical Professor, UCSD), has enrolled two patients. According to Kipps, both patients have experienced extremely rapid responses to the gene-immune therapy and have achieved complete remission.

Kipps is hopeful that this study will markedly improve the outlook for CLL patients. “The successful completion of the proposed clinical study and correlative science will provide a better understanding of the mechanisms related to anti-cancer treatment resistance in leukemia/lymphoma cells and the potential application of this novel chemo-sensitization strategy not only in CLL, but in other cancers as well. But even more importantly, this meets an acute need in patients who are not given many options to get treated and to enter remission,” says Kipps.



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