

# LYMPHOMA

RESEARCH • FOUNDATION

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RESEARCH REPORT

September, 2005; Vol. 3, No. 2

## *LRF RESEARCH GRANT PROGRAM REPORT*

*Understanding the variety of blood cancers known as lymphomas is essential to developing treatments and cures and improving the outcome for patients. In order to achieve those ends, the LRF supports research in a variety of ways. With the help of our distinguished Scientific Advisory Board, made up of many leaders in the field, we fund Fellowships and Clinical Investigator Career Development Awards each year. The following synthesizes reports from our 2004 and 2003 grant recipients.*

### **Clinical Investigator Career Development Awards**

Each year the LRF funds Clinical Research projects that test new therapies. This program enables investigators to learn how to conduct clinical trials and to identify new treatment options and compare them to existing therapies to determine the most effective options for patients. These awards also support the development of physicians as scientists, enhancing their understanding of lymphoma, their research skills and therefore our ability to meet the challenge of finding a cure.

◆ **Dr. John Pagel of the Fred Hutchinson Cancer Research Center**, a recipient of a 2004 Clinical Investigator Career Development Grant describes his study as an effort to reduce the toxicity of conventional radioimmunotherapy. Radioimmunotherapy works by using an antibody molecule with an attached radioactive isotope that binds specifically to a target site (in this case the CD20 protein) on the surface of a cancer cell and delivers a toxic dose of radiation to that cell and nearby tumor cells. It has been shown to be an effective treatment for lymphomas. However, radio-labeled antibodies that have not bound to cancer cells can have toxic effects on normal tissue.

Dr. Pagel and his colleagues are testing a

“pre-targeting” method. Patients would be treated with a CD20 antibody that has been linked to a molecule called streptavidin. This is followed by a clearing agent that removes antibody-streptavidin molecules that have not bound to cells from the circulation. The patients would then be treated with a radioactive biotin preparation. Biotin binds strongly to streptavidin thus linking the radioactive isotope to the cell surface.

Dr. Pagel’s preliminary studies have shown that this pre-targeted approach appears significantly superior to conventional one-step radio-labeled antibody therapy with the promise to improve remission rates, durations and survival for these diseases. His studies have documented the feasibility and safety of this treatment and he believes that this approach offers the potential to improve the cure rate of patients with relapsed NHL, which currently kills about 18,000 Americans each year.

◆ Another recipient of a 2003 Clinical Investigator Career Development Grant, **Dr. John M. Timmerman** of **UCLA**, is studying the immunotherapy of lymphoma using idiotypic-loaded dendritic cells ⌘. Dr. Timmerman and his associates have previously demonstrated that a new type of therapeutic lymphoma vaccine can shrink tumors in patients with follicular lymphoma. This vaccine consists of special immune-stimulating white blood cells, called dendritic cells, loaded with a unique protein (called “idiotypic”) that is isolated from each

patient's tumor cells. These dendritic cells serve to "jump-start" the immune system to recognize and destroy cancer cells. Dr. Timmerman now plans to administer larger doses of these cells, along with "booster" injections of the idiotype protein and the immune stimulant GM-CSF in an attempt to induce tumor shrinkage in a higher proportion of lymphoma patients. Further refinements in this tumor-specific, individualized vaccine may lead to lymphoma treatments that selectively attack tumor cells, leaving normal tissues unharmed.

## Fellowships

The LRF's **Two-Year Fellowships** uniquely permit the uninterrupted development of promising leads and help attract the nation's best scientific talent to careers in lymphoma, thereby ensuring the new generation of physician-scientists dedicated to the care of lymphoma patients and developing improved care, treatments and a cure. Their emphasis upon translational as well as purely basic research assures that breakthroughs are quickly transformed into viable treatment options. The following brief reports give some insight into the complexities and challenges of lymphoma research and the creative and dogged determination of the researchers.

◆ **Dr. Jean Marie Bruey**, an LRF Fellow at the **Burnham Institute**, is studying the expression and function of a protein called NAC in leukemia and lymphoma. NAC protein plays a role in the regulation of apoptosis (genetically programmed cell death). During the last year of work funded by LRF, Dr. Bruey has confirmed that NAC controls pathways of relevance to lymphoma and leukemia. Given the increasing incidence of lymphoid malignancies and the frequent development of resistance to the available treatments, it is of the utmost importance to find new targets for drug development that can result in new therapeutic approaches. Specifically, NAC promotes cell death, so enhancing its function would encourage lymphoma and leukemia cells to die. Dr. Bruey and her colleagues are working hard to define the molecular signaling pathways involving NAC with the goal of finding ways to activate the NAC protein in malignant B cells.

***The mission of the Lymphoma Research Foundation is to eradicate lymphoma and serve those touched by the disease.***

◆ Another fellow, **Dr. Matthew Glenn** at **Yale University**, is studying the novel inhibitors of STAT signaling as potential selective anti-cancer therapies. Many cancers have overly active proteins known as STATs, which in normal cells shuttle extra-cellular signals to the nucleus where they promote production of proteins responsible for cell survival and growth. In normal cells STAT activation is rapid and transient. However many cancers have mutations that persistently activate STAT, generating a continuous growth and survival signal that promotes the development of the cancer. Dr. Glenn's project is developing agents that prevent STAT function to determine whether this protein is a viable drug target. Over the past year he and his colleagues have used computer simulations to predict the structures of molecules that could in activate STATs. These models have been used to develop physical compounds that can prevent STAT function and consequently selectively kill cancer cells with persistently activated STATs, while not killing normal cells. This represents a successful first step towards developing new treatments for lymphoma and leukemia that have incorrectly regulated STATs.

◆ The main focus of the work of **Dr. Andreas Krueger**, a fellow at the **Dana-Farber Cancer Institute**, is attempting to understand the mechanisms that govern

the development of the immune system—in particular the roles of molecules that regulate developmental programs in T cells. In order to become fully functional, T cells have to pass several checkpoints. At these checkpoints different molecules must act closely together to allow cells to progress in their developmental program. Abnormal function of these molecules is the cause of T cell acute leukemia, a common malignant disease in children and adults. Dr. Krueger's studies concentrate on the interplay of such molecules in both normal T cell formation and tumor formation. Using techniques of molecular biology and immunology Dr. Krueger's laboratory has analyzed how one molecule, Notch, critically impacts many stages of T cell development. Malfunction of Notch has been shown to occur in half the cases of T cell acute leukemia. Dr. Krueger's studies have revealed some of the molecular mechanisms involved in this development of T cells into tumor cells and will continue to investigate the interplay of Notch with other molecules in tumor formation.

◆**Dr. Paul Norman**, a fellow at the **Stanford University School of Medicine**, is examining the impact of natural killer cell variation on lymphoma and transplantation therapy. Natural killers are an immunologically powerful type of white blood cell known to be important during transplantation therapy for lymphomas. They are regulated by a newly discovered protein family called killer cell immunoglobulin-like receptors or KIRs. Because KIRs interact with the classical transplantation molecules (known as HLA) Dr. Norman and his colleagues are constructing a high-resolution map of their genetic region. This will allow them to refine the criteria for choosing suitable transplantation donors and reduce the incidence of immunological complications such as rejection or graft-versus-host-disease.

◆A fellow at the **University of California at San Diego**, **Dr. Bradley Todd Messmer** is studying the antigen receptors used by B-CLL cells. B-cell chronic lymphocytic leukemia (B-CLL) is a very prevalent, incurable adult leukemia. The leukemia cells from each B-CLL patient have an antibody on their surface that serves a critical function for the cell. Although these antibodies are structurally unique in individual normal B lymphocytes, they may be very similar in different B-CLL patients. Dr. Messmer has used molecular techniques to produce large quantities of these antibodies so that he can identify small molecules that bind to them. Furthermore he and his colleagues have identified more cases of CLL patients with very similar antibodies, suggesting a previously unexpected mechanism of leukemia development.

◆**Dr. Masahiro Yoshimura**, **Harvard University**, reports that since many human diseases are caused by inappropriate protein production or altered protein

function, his project focuses on a novel strategy for developing unique molecular entities that would target RNA specifically. Traditional drugs are designed to interact directly with proteins. This new approach uses drugs to inhibit the production of disease-causing proteins; it would be more selective and therefore less toxic. It works by exploiting the phenomenon of “surface borrowing” in which a small molecule is presented to RNA in a complex with a protein, expanding the overall surface area available for interaction with RNA. Dr. Yoshimura and his group have created a system by which to target the binding of a small molecule/protein complex to RNA and they expect to find it a useful tool for studying gene expression and protein function.

◆**Dr. Alice Fan**, **Stanford University**, explains that several human non-Hodgkin’s lymphomas arise when oncogenes are present at abnormally high levels. MYC and BCL2 are the names of two such oncogenes. Burkitt’s lymphomas occur when MYC is at high levels. Follicular lymphoma occurs when the BCL2 oncogene is too high. Using mice in which she can control levels of these oncogenes, Dr. Fan turns up their levels causing the mice to develop lymphoma. She is exploring if restoring normal levels of oncogenes can cure these lymphomas. When mice develop lymphoma from excess levels of MYC, turning MYC levels back down to normal can cure 50% of the mice. In contrast, preliminary studies show that when mice develop lymphoma from excess levels of BCL2, turning BCL2 levels back down to normal does not cause the lymphomas to regress. Thus BCL2 by itself may not be a good target for therapy in these mice. In actuality, most human tumors are complicated and have abnormally high levels of more than just one oncogene. In mice, more complicated lymphomas can be imitated by turning up both MYC

## GLOSSARY OF TERMS

**A Dendritic cell** is part of your immune system and is a cell that captures antigens (foreign substances capable of provoking an immune response) and migrates to the lymph nodes, and spleen, where it presents the processed antigens to T-Cells.

**RNA**, or ribonucleic acid, is a macromolecule concerned in the control of normal cellular processes, especially protein synthesis; RNA is found in all cells of the body.

**Oncogenes**. Any of a family of genes, which under normal circumstances code for proteins involved in cell growth or regulation but may foster malignant processes if mutated or activated. Oncogenes often work in concert to turn cells into cancer, and their action may be exacerbated by retroviruses, jumping genes or inherited mutations.

**In vitro** refers to a process or study occurring in an artificial environment as in a test tube or culture media.

**In vivo** refers to a process or study occurring in the living body.

**NPM-ALK** is a fusion protein associated with anaplastic large cell lymphoma, it represents a chromosomal translocation associated with the gene for a protein NPM and a possible oncogene known as ALK.

**P53** is a tumor suppressor gene.

and BCL2 oncogenes together. When this is done, the mice develop even more aggressive lymphomas. Further, when Dr. Fan turns off both MYC and BCL2, the complicated lymphomas regress, and this maneuver prolongs survival. However in these complicated lymphomas, despite a complete initial remission, the complicated lymphomas inevitably return and it is much more difficult to obtain a cure by just restoring normal levels of the two oncogenes. These sophisticated mouse models show how targeting single or multiple oncogenes may be useful in the treatment of lymphoma.

◆**Dr. Michaela Liedtke** has been working to establish in vitro and in vivo models of human anaplastic large cell lymphoma to study lymphomagenesis and facilitate the development of novel therapies. Working at the **Stanford University School of Medicine**, Dr. Liedtke has established a retroviral transduction system to enforce expression of NPM-ALK in cord blood cells. She is working to characterize the NPM-ALK and demonstrated that NPM-ALK enhances the self-renewal and clonogenic potential of the affected cells compared to normal cells. Her next step will be to develop a mouse model that will form the basis for an expanded understanding of how these lymphomas develop and potentially how they can be treated.

◆Alpha 4 is a protein that is highly expressed in lymphocytes. When alpha 4 function is lost, lymphocytes undergo cell death. With that in mind, **Dr. Mei Kong** of the **University of Pennsylvania** has hypothesized that deregulation of alpha 4 function will contribute to development of lymphoma. Dr. Kong is exploring the function and molecular mechanism of alpha 4 in the regulation of lymphocyte survival and death. She has found that alpha 4 is required to prevent cell death and that it is an essential regulator of the tumor suppressor, p53. Without alpha 4 protein the activity of p53 is increased, while over expression of alpha 4 leads to inhibition of p53 and decreased cell death. This suggests that alpha 4 may play a role in the development of tumors and could be a new avenue for treating lymphomas.

***For more on the work of LRF fellows and clinical investigators, watch for future progress reports in the Research Report newsletter.***

***The Lymphoma Research Foundation  
is pleased to recognize  
Millennium Pharmaceuticals  
for providing an unrestricted  
educational grant to  
support this publication.***

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