

LYMPHOMA

RESEARCH • FOUNDATION

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RESEARCH REPORT

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LRF GRANT RECIPIENTS MAKE IMPRESSIVE PROGRESS

The Lymphoma Research Foundation is a leader in supporting the recruiting and training of junior scientists for careers in lymphoma. LRF training award programs help develop future leaders in the fields of lymphoma research and clinical care.

Training support is provided through two award mechanisms: LRF Fellowships and LRF Clinical Career Development Awards. LRF Fellowships are 2-year grants designed to enable junior faculty to engage in lymphoma research under the guidance of a Mentor/Sponsor. Applicants may be awarded up to \$105,000 over 2 years. LRF Clinical Career Development Awardees participate in a 3-year program, learning how to develop new therapeutics and diagnostic tools for lymphoma under the guidance of experienced investigators. Award recipients may receive funds up to a maximum of \$225,000 over 3 years.

LRF CLINICAL CAREER DEVELOPMENT AWARD 2005 – 2008

◆ Ann LaCasce, MD, of the Dana Farber Cancer Institute in Boston, is an LRF Clinical Career Development Award Recipient. Dr. LaCasce is working on a project studying the cellular protein NFκB as a potential target for developing new treatments for mediastinal large B-cell lymphoma and diffuse large B-cell lymphoma.

Dr. LaCasce has, in her first year of three, made progress developing a panel of genes that are expressed differentially in MLBCL and DLBCL. These results were reported in the *American Journal of Surgical Pathology*. In addition, she characterized the expression of the protein NFκB

in these lymphomas. She confirmed that NFκB is expressed much more highly in MLBCL than in DLBCL. This means that NFκB-inhibitors have potential as a therapy for MLBCL.

These studies by Dr. LaCasce, her mentor and her colleagues, establish the rationale to proceed with a Phase II clinical trial in MLBCL patients testing NFκB-inhibitors. Many NFκB inhibitors are being developed by biotechnology and pharmaceutical companies. Currently, Velcade (Millennium Pharmaceuticals) is one inhibitor that has been approved by the F.D.A. for use in a different blood cancer, multiple myeloma.

2004-2006 Recipients

◆ Alice Fan, PhD, of the Stanford University School of Medicine in California, studies non-Hodgkin's lymphomas that arise when cancer genes such as MYC or BCL2 are present at abnormally high levels. Burkitt's lymphoma occurs when MYC is at high levels. Follicular lymphoma (FL) occurs when excess BCL2 is present. Using mouse models of lymphoma in which levels of different cancer genes can be controlled, Dr. Fan is exploring whether restoring normal levels of cancer genes can cure lymphomas in mice. When the mice develop lymphoma from excess levels of MYC, turning MYC levels back down to normal can cure lymphomas in 50% of the mice, and increase overall survival. In contrast, when mice develop lymphoma from excess levels of BCL2, turning BCL2 levels back down to normal levels does not cause regression. Thus BCL2 by itself may not be a good target for therapy in these mice.

◆ Jean Marie Bruey, PhD, of the Burnham Institute in La Jolla, California, has characterized the genes BCL-2 and NAC, and their interactions in CLL and FL. She studied how these genes are expressed in cell lines in the laboratory and in primary patient samples. In several samples from CLL patients, she found differential expression in differing forms of CLL (non-aggressive versus aggressive CLL). She has partnered with the CLL consortium to obtain patient samples and is working to examine the gene changes in 100 samples over the next year. In addition, she will continue to study these genes in FL. Her preliminary work has been submitted for publication in *Cell*.

◆ Michaela Liedtke, PhD, at Stanford University, is developing a model to recapitulate the development of anaplastic large cell lymphoma, a subtype of lymphoma that is caused by a chromosomal translocation that results in the expression of the NPM-ALK fusion protein. Using lab techniques known as retroviral constructs, the group established an experimental system expressing the NPM-ALK protein in CD34- positive human cord

blood cells. The Stanford team has demonstrated that cord blood cells expressing NPM-ALK gain properties necessary for malignant transformation in lymphoma. They are also developing an animal model system by the transplant of NPM-ALK expressing CD34+ cord blood cells into NOD/SCID mice. This murine model of human anaplastic large cell lymphoma can then be used to assess the efficacy of novel therapies.

◆ Paul Norman, PhD, at the Stanford University School of Medicine, is developing methods to improve the safety and success of transplantation therapy for lymphomas. He is studying "natural killer (NK) cells" that form a crucial component of our immune system and have an important role during transplantation therapy. These cells interact with the classical transplant matching molecules (the HLA Tissue Type) and regulate a person's immune response to the donor cells. Dr. Norman has established that the natural killer cell surface proteins responsible for this recognition vary between people. In the future, "typing" the protein expression on these NK cells will, just like HLA typing, aid in finding suitable donor-to-recipient matches. Through the combined research efforts of Dr. Norman and other researchers worldwide, it will soon be possible to predict the optimal donor-recipient pairings for transplantation. Dr. Norman and his colleagues have designed and developed an efficient and cost-effective assay for this important purpose.

2005-2007 Recipients

◆ Wei Ai, MD, PhD, of the Stanford University School of Medicine, is a 2005 award recipient, and *The Lisa Beth Fishman Memorial Fellow*. She has developed a novel treatment that will trigger the patient's own immune system to recognize lymphoma cells as enemies and to mount an immune response to attack them. This experimental immune treatment consists of radiation of a local tumor followed by injecting a new immune stimulant, CpG into the irradiated tumor site. The team will test how safe this regimen is in a clinical trial. They have treated 5 patients with FL, among which 3 had stable disease and one patient experienced partial tumor

regression. The fifth patient is still being treated. Dr. Ai's team also treated 2 patients with skin lymphoma; one of them had a stable disease, the other has shown some tumor regression already, even though he has not yet finished all his treatments. The treatment appears safe and well tolerated. Over the next year, Dr. Ai will continue the study, with the goal of recruiting a total of 15 patients.

◆ Irene Ghobrial, MD, of the Dana Farber Cancer Institute in Boston, is conducting a Phase II clinical trial with the novel mTOR inhibitor RAD001 (Everolimus, Novartis) in aggressive lymphomas, indolent lymphomas and rare lymphomas (T cell and Waldenstrom's). Fifty patients have been enrolled to date. RAD001 appears to be safe and well tolerated in these lymphoma patients. Further analyses are needed, as well as recruitment of additional patients, to begin to determine how effective the drug is and the response rates in patients. While conducting this trial, the group also began studies on a new drug, perifosine, which targets a different part of the same molecular pathway as RAD001. They have shown in lab studies that combinations of these drugs may be more effective than a single one. They will begin testing perifosine in the rare lymphoma Waldenstrom's Macroglobulinemia.

◆ Ramune Reliene, PhD, at UCLA, is The *Elizabeth Banks Jacobs & Bryon Wade Strunk Memorial Fellow*. She is studying a model in the lab, termed Atm mice, which spontaneously develop lymphoma.

Her goal is to test whether dietary antioxidants can prevent genetic damage and lymphoma development in these mice. The group gave antioxidant-supplemented drinking water to the experimental mice. Preliminary data show that antioxidants reduce genome damage in Atm mutant mice, suggesting that long-term antioxidant dietary supplementation may act as a lymphoma preventive.

◆ Frank Rosenbauer, MD, of the Harvard Medical School in Boston and the Max-Delbrueck-Center for Molecular Medicine in Berlin, Germany, is studying a gene involved in both blood cell development and in T-cell lymphoma. When the expression of the transcription factor, termed PU.1, is altered in mice, the mice develop T-cell lymphoma. Identification of the key regulatory DNA-elements of the PU.1 gene, as well as other genes that alter its expression, will be crucial events for the development of T-cell cancer. The PU.1 gene and interacting pathways provide novel targets to develop therapeutics for T-cell lymphomas.

◆ Qinyan Yin, PhD, of Tulane University, is studying the role of the Epstein Barr Virus (EBV) as a potential underlying mechanism promoting tumor development in lymphoma. She is utilizing techniques known as "siRNA" to inhibit genes involved in EBV latency, or long-term expression. In cell culture models in the laboratory, Dr. Yin was able to inhibit these EBV-associated genes and suppress EBV-positive tumor cell growth and survival. These

LRF Fellows	Institution	Area of Study
2004-2006 Recipients		
Jean Marie Bruey, PhD	Burnham Institute	CLL and FL
Alice Fan, MD, PhD	Stanford University School of Medicine	Burkitt's and FL
Michaela Liedtke, PhD	Stanford University	Anaplastic large cell lymphoma
Paul Norman, PhD	Stanford University School of Medicine	Transplantation therapy for lymphomas
2005-2007 Recipients		
Wei Ai, MD	Stanford University School of Medicine	Low grade FL, skin lymphoma
Ramune Reliene, MD, PhD	University of California Los Angeles	Antioxidants in lymphomas
Frank Rosenbauer, MD	Harvard Medical School	T-Cell lymphomas
Qinyan Yin, PhD	Tulane University	Epstein Barr Virus (EBV) in lymphomas
Xin Yu, PhD	The Rockefeller University	B-Cell lymphomas

data suggest that siRNAs against EBNA1 may have therapeutic value in EBV-associated diseases. These findings may one day have a role in a number of human cancers including nasopharyngeal carcinoma, Hodgkin's lymphoma, and non-Hodgkin's lymphomas (NHLs).

◆ Xin Yu, PhD, of the Rockefeller University in New York, is studying the interactions of gene pathways in B-cell development and their role in B-cell lymphomas. She has discovered novel interactions of two proteins, named OCA-B and galectin-1. The discovery adds significantly to the understanding of galectin function in B-cell proliferation/differentiation. The results were published this summer in the *Journal of Biological Chemistry*. Dr. Yu's ongoing studies are very novel and potentially significant in understanding B-cell biology and lymphomagenesis.

Glossary

Mouse model: A laboratory mouse useful for medical research because it has specific characteristics that resemble a human disease or disorder. Strains of mice having natural mutations similar to human ones may serve as models of such conditions. Scientists can also create mouse models by transferring new genes into mice or by inactivating certain existing genes in them.

RNA: Ribonucleic acid is one of the two types of nucleic acids found in all cells. The other is deoxyribonucleic acid (DNA). RNA transmits genetic information from DNA to proteins produced by the cell.

siRNA: Abbreviation for "small inhibitory RNA", a short sequence of RNA that can be used to silence gene expression.

Transcription: In biology, the process by which a cell makes an RNA copy of a sequence of DNA that is a gene.

The Lymphoma Research Foundation

Thanks all of our generous donors who have done so much to grow The LRF Research Program.

Your generosity saves lives today, tomorrow and always.

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Thank You

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