

Research Report

VOLUME 5, No. 2

SEPTEMBER 2007

LRF Grantees: Updates & Interviews

Through the years, the Lymphoma Research Foundation (LRF) has supported some of the nation's best emerging scientific talent. Recipients of LRF's Fellowships, Career Development Awards, and Special Initiative grants have made significant contributions to the field of lymphoma research.

This report provides an update on some of their discoveries and fills you in on some of the recent news from LRF and the field.

Lymphoma Research Foundation Fellowships

Since 1992, LRF has been awarding two-year Post-Doctoral Fellowship grants to young professionals interested in pursuing a career in lymphoma research. These fellowships allow the best and brightest post-doctoral scientists to hone their research skills and become the next generation of lymphoma researchers. To date, LRF has provided 200 fellowships to researchers across the nation.

The following section contains in-depth interviews with Drs. Irene Ghobrial and Jia Ruan, two talented physicians whose contributions are actively advancing the field of lymphoma research.

Inside this Issue

Interview with Dr. Ghobrial.	2
Interview with Dr. Ruan.	3
2005 LRF Fellows.	4
Career Development Awards.	5
Recent News from the Field.	5
What's New at LRF?.	7

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.

For more information, visit:

www.lymphoma.org

www.mantlecelllymphoma.org

www.clinfogroup.org

LYMPHOMA
RESEARCH • FOUNDATION

Irene M. Ghobrial, M.D. Dana-Farber Cancer Institute, Boston, MA

We recently caught up with Dr. Irene Ghobrial, a 2005 fellowship graduate, to discuss her research and the impact the fellowship had on her career. Dr. Ghobrial received an LRF Fellowship award for studying the role of the PI3K pathway in non-Hodgkin lymphoma.

After completing medical school at Cairo University in Egypt and a residency at Wayne



Dr. Irene Ghobrial

State University, Dr. Ghobrial accepted a fellowship at the Mayo Clinic in Rochester, Minnesota. It was at the Mayo Clinic where she became interested in laboratory research and studying Waldenstrom's

Macroglobulinemia (WM), a rare incurable lymphoma with limited options for therapy. "Waldenstrom is very exciting to me. The drive to find a cure for these patients is what keeps me going," stated Dr. Ghobrial.

At the time of her award, Dr. Ghobrial was an Assistant Professor at the University of Pittsburgh. She focused her research on a specific biological pathway (PI3 kinase/Akt pathway) that controls tumor cell growth, motility, and survival. Her laboratory started testing several drugs that target this pathway: RAD001, perifosine, and enzastaurin.

Based on the promising results that were discovered in the laboratory, Dr. Ghobrial began initiating clinical trials of these cancer

therapies. To date, phase II clinical trials are underway for RAD001 and perifosine. In fact, the phase II trial of RAD001 showed such great response rates that it was expanded to include 25 more patients with WM. Next year, she will initiate a clinical trial for enzastaurin.

According to Dr. Ghobrial, "The preclinical evaluation of perifosine and enzastaurin was the first in evaluating an agent in vitro and in vivo, specifically using WM cells and patient primary cells, and taking the observations into clinical trials." If these drugs complete all of the clinical trial phases, continue to produce positive results, and are approved by the FDA, they could be the very first FDA-approved drugs for WM.

Today, Dr. Ghobrial is an Instructor of Medicine at the Dana-Farber Cancer Institute where she continues to conduct preclinical studies to examine the pathogenesis of WM and possible new therapeutic options for this disease. She is also exploring the mechanisms surrounding the migration of cancer cells into the bone marrow and lymph nodes.

The LRF Fellowship grant allowed Dr. Ghobrial to make valuable discoveries in the field of lymphoma and gave her the experience and recognition necessary to continue her research. Dr. Ghobrial expressed her appreciation for receiving the LRF grant and enthusiastically stated, "It really pushed my career forward."

Waldenstrom's Macroglobulinemia: is a rare, indolent (slow-growing) non-Hodgkin lymphoma. There are approximately 1,500 new cases annually in the United States. *National Cancer Institute*

Jia Ruan, M.D., Ph.D.
Weill Medical College of Cornell
University, New York, NY

Dr. Jia Ruan received an LRF Fellowship award in 2006 for studying lymphoma neo-angiogenesis and anti-angiogenic therapy. Although Dr. Ruan will officially complete her fellowship in 2008, her research findings to date have shown tremendous promise.

Dr. Jia Ruan started her research career at Cornell University where she completed a



Dr. Jia Ruan

combined MD/PhD program. After completing a fellowship in hematology at Stanford University, she came back to Cornell to complete her oncology training. It was at this time that she became interested in clinical trials and research

involving hematological malignancies.

Upon receiving the LRF award, Dr. Ruan sought to, “understand both the biology and therapeutic potential of angiogenesis [blood vessel formation] in lymphoma disease.” She has done so by conducting both translational and clinical studies.

In one of Dr. Ruan’s translational studies, she characterized a particular subset of bone marrow-derived cells (VEGFR-1+CD68+ hematopoietic cells) that contribute to blood vessel formation in human lymphoma patients. She is now working to define the way in which these cells are recruited and how they influence the formation of blood vessels.

Under the mentorship of Dr. John Leonard, Dr. Ruan is also studying novel combination therapies that involve standard chemotherapy mixed with anti-angiogenic agents that block the growth of blood vessels that nourish tumors. One promising therapy currently in a Phase II clinical trial, involves low dose chemotherapy (PEPC plus rituximab) in combination with an anti-angiogenic agent called thalidomide. According to Dr. Ruan, “We have applied this approach to patients with relapsed mantle cell lymphoma and have witnessed a significant therapeutic effect.”

Based on the success of the first clinical trial, Dr. Ruan is now proposing to examine the effect of bevacizumab (an anti-angiogenic agent) combined with standard CHOP plus rituximab in patients newly diagnosed with mantle cell lymphoma.

Her team is also examining the effect of the anti-angiogenic therapy on the level of circulating progenitor cells (cells that will contribute to blood vessel formation) in patients with non-Hodgkin lymphoma.

Dr. Ruan is currently an Assistant Professor of Medicine at Weill Medical College and an Assistant Attending Physician at New York Presbyterian Hospital. Within the last year, Dr. Ruan has begun collaborating with Dr. Katherine Hajjar (Cell & Developmental Biology Department) to examine the role of Annexin 2 (A2) in lymphoma angiogenesis. The experiments have already generated substantial preliminary data.

Dr. Ruan feels that the LRF Fellowship played a crucial role in her professional development and allowed her to actively craft her research focus. In speaking to the Research Report, she said, “The LRF Fellowship grant provides protected research time which is critical for junior faculty who have just started their career.”

2005 LRF Fellows: Final Reports

The following section highlights the research completed by LRF's 2005 fellows.

Ramune Reliene, Ph.D., University of California, Los Angeles, CA

The major goal of Dr. Reliene's study was to understand whether antioxidants can prevent lymphoma. Dr. Reliene performed her study with a synthetic non-toxic antioxidant called N-Acetyl Cysteine (NAC). Mice (also known as *Atm*-deficient mice) were randomly divided into two groups: one group was given drinking water supplemented with NAC and the other group drank normal water. Dr. Reliene discovered that the mice receiving NAC-treated water had significantly lower levels of damage to their DNA. Science has already revealed that DNA damage can lead to the formation of cancer. Thus, these results show that NAC may reduce the rate of lymphoma in these mice by providing a protective effect against DNA damage. Dr. Reliene has indicated that this study could be directly applied to patient care, as NAC is safe to use in humans. In the future, Dr. Reliene would like to determine whether antioxidant-rich food, such as fruits or vegetables, can prevent lymphoma in these mice.

Antioxidant: a substance that protects cells from the damage caused by free radicals. Antioxidants include beta-carotene, lycopene, vitamins A, C, and E, and other natural and manufactured substances. *National Cancer Institute*

Frank Rosenbauer, Ph.D., Max-Delbrueck Center for Molecular Medicine, Berlin, Germany

Dr. Rosenbauer is conducting his research on factors that regulate the development of blood cells. Most of his research has focused on a specific transcription factor called PU.1. A transcription factor is a protein that can control whether specific genes are turned on or off, and the PU.1 transcription factor is essential for the development of all lymphocytes, including T-cells. Dr. Rosenbauer was able to create mice that were missing a portion of their DNA (specifically, URE – Upstream Regulatory Element) that controlled PU.1 production. Consequently, normal T-cell development is disrupted in these mice, leading to the development of aggressive T-cell lymphomas. His studies have also revealed that PU.1 is controlled by a specific biological pathway (wnt-pathway), which plays a critical role in many human cancer types. Finding a way to disrupt this pathway could potentially prevent the development of T-cell cancers.

Qinyan Yin, Ph.D., D.V.M., Tulane Health Sciences Center, New Orleans, LA

Dr. Yin has focused her research on lymphomas related to the Epstein-Barr virus (EBV). EBV is a virus that causes mononucleosis, and it has also been closely associated with various forms of lymphoma. Dr. Yin has used certain agents, called siRNAs (small inhibitory RNAs), to alter genes that control the growth and survival of EBV in tumors. To date, this approach has shown a lot of promise. Dr. Yin has begun identifying additional cellular targets that are highly expressed in many lymphomas and that are induced by EBV. Dr. Yin will continue her investigations into this area and is hopeful that these studies will some day lead to the development of new cancer drugs and therapies.

Career Development Awards

LRF also provides Career Development Awards (CDA) 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 provided 10 Clinical Development Awards.

The following section highlights the research conducted by two CDA graduates, Dr. John Pagel, a 2004 CDA recipient, and Dr. Ann LaCasce, a 2005 CDA recipient.

John Pagel, M.D., Ph.D., Fred Hutchinson Cancer Research Center, Seattle, WA

Dr. Pagel's laboratory has been working to improve the efficacy of radioimmunotherapy (RIT) for non-Hodgkin lymphoma (NHL). RIT is an exciting new therapy that delivers radiation directly to cancer cells using radiolabeled monoclonal antibodies (an antibody that has been combined with an agent capable of emitting radiation). The radiolabeled antibody binds to the surface of cancer cells allowing it to deliver a dose of radiation directly to the cancer cell.

In his studies, Dr. Pagel has compared traditional RIT with a "pretargeted" RIT. Pretargeted RIT utilizes an antibody that can bind to a cancer cell and a radioactive agent. The antibody is administered first. This gives the antibody time to attach itself to cancer cells. A clearing agent is then administered to get rid of any excess antibody. Lastly, the radioactive agent is administered and it binds to the antibody on the cancer cell.

In his final report, Dr. Pagel revealed that the pretargeted approach significantly improved pre-clinical remission rates, remission duration, and survival for NHL. The pretargeted approach also improved the

delivery of radiation to tumor cells and decreased radiation exposure to normal cells. He hopes to initiate a clinical trial with this novel therapy in the near future.

Ann LaCasce, M.D., Dana-Farber Cancer Institute, Boston, MA

According to her interim report, Dr. LaCasce initiated a Phase II clinical trial examining the effect of adding Velcade to the standard chemotherapy (CHOP/Rituxan) used for Mediastinal large B-cell lymphoma (MLBCL), a rare type of lymphoma which predominantly affects young women. Velcade works by blocking a specific pathway (NFkB pathway) critical for the growth and survival of tumor cells. Due to the positive results seen thus far, Dr. LaCasce has begun researching additional agents that block this pathway and hopes to study them in clinical trials as well.

Recent News from the Field

New Targets for Therapy

Researchers have discovered some new targets which may lead to novel therapies for lymphoma. Following are some recent findings.

◆ Three newly developed Src/Abl kinase inhibitors (AZM559756, AZD0530, and AZD0424) are able to induce cell death and prevent cell replication in certain lymphoma cell lines. These results imply that Src/ABL kinase inhibitors could be a new way to combat lymphoma.¹

◆ Researchers at the National Cancer Institute have recently discovered genes that are over-expressed in blood vessels that feed tumors in mice and humans. These genes represent important targets for the development of new drugs because they do not affect blood vessel growth (angiogenesis) in healthy tissues.²

◆ University of Pennsylvania scientists have discovered that an over-expression of PAX5 (a B-cell activator) in B-cell lymphoma cells increased tumor cell growth when transplanted into mice.⁵

Advances in Treatment

Many researchers and pharmaceutical companies are in the process of testing new cancer drugs or combinations of therapies which have been showing positive results. Following are a few recent developments.

◆ Researchers in China recently examined the anti-tumor activity of rituximab combined with suberoylanilide hydroxamic acid (SAHA). Researchers discovered that this combination significantly promoted cell death in B-cell non-Hodgkin lymphoma (NHL) cells.⁴

◆ According to a phase II clinical trial, adding Zevalin plus extended dose rituximab (Zevalin/R) to a short course of CHOP plus rituximab (CHOP-R) increases complete response rates among patients with follicular non-Hodgkin lymphoma.⁵

◆ A combination of rituximab, gemcitabine and oxaliplatin (R-GemOx) shows promising response rates with acceptable toxicity in patients with relapsed or refractory B-cell lymphoma who are not eligible for high-dose therapy. Patients receiving four cycles of R-GemOx had an overall response rate of 83%.⁶

◆ Research has shown that two cycles of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) followed by EF-RT (extended-field radiotherapy) is more effective than EF-RT alone.⁷

◆ Denmark's Genmab and GSK have recently announced plans to expand the use of HuMax-CD20, a human monoclonal antibody, for large B-cell lymphoma. They are also in the process of planning Phase III

studies of HuMax-CD20 in CLL and follicular NHL. It is already in late-stage development for positive B-cell chronic lymphocytic leukemia.⁸

◆ ProNAi Therapeutics, Inc. has just announced its first “mechanism of action studies” for the oncology drug called PNT2258. To date, PNT2258 has demonstrated anti-tumor activity in non-Hodgkin lymphoma in preclinical studies with mice. ProNAi anticipates filing for Investigational New Drug status for PNT2258 in late 2007.⁹

◆ Kiadis Pharma has completed a Phase II clinical trial of Reviroc, a drug used to eliminate cancer cells for patients receiving an autologous transplant (a procedure which uses a patient's own bone marrow to serve as a transplant) for end-stage blood cancer. Based on the positive results, Kiadis Pharma will now implement a phase III study.¹⁰

1. Src kinase inhibitors induce apoptosis and mediate cell cycle arrest in lymphoma cells. *Anti-Cancer Drugs*. 18(9):981-995, October 2007. Washington U., St. Louis; Georgetown U. Hospital Center.
2. *Cancer Cell*, Vol.11, Issue 6.
3. *Journal of Clinical Investigation*. Published online August 24, 2007.
4. Combined effects of histone deacetylase inhibitor and rituximab on non-Hodgkin's B-lymphoma cells apoptosis. *Exp Hematol*. 2007 Aug 1.
5. *Oncology News International*, Vol. 16, Number 8, August 2007.
6. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. *Annals of Oncology* 2007 18(8): 1363-1368.
7. *Journal of Clinical Oncology*, Vol. 25, No. 23, 2007: pp. 3495-3502.
8. Can be found online at www.genmab.com
9. Can be found online at www.pronai.com/news
10. Can be found online at www.kiadis.com/news

What's new at LRF?

Mantle Cell Lymphoma Clinical Trials Database

The Lymphoma Research Foundation's Mantle Cell Consortium has successfully developed a database of clinical trials specifically focusing on mantle cell lymphoma. The clinical trials can be found on the LRF website at www.mantlecelllymphoma.org, by clicking on the sitemap and selecting "Search Clinical Trials." The clinical trials listed are updated periodically. The list is not comprehensive, nor exhaustive, and the LRF does not specifically recommend one trial over the other. The LRF strongly encourages interested patients to talk to their own physician before participating in a clinical trial.

Mantle Cell Lymphoma Cell Bank

The Lymphoma Research Foundation is using this opportunity to announce the creation of a Mantle Cell Lymphoma (MCL) Cell Bank. The Cell Bank is a collection of various MCL cell lines created by scientists from all over the world. The purpose for creating the Cell Bank is to provide a single, centralized location where scientists can go to acquire MCL cell lines to accelerate discoveries in mantle cell lymphoma.

The Cell Bank is housed at ATCC (www.atcc.org), the world's largest biological resource center. The ATCC will be responsible for acquiring, characterizing, maintaining, and distributing all of the cell lines. Rigorous procedures will be performed on each cell line to ensure quality and consistency.

To date, the Cell Bank contains 5 cell lines. However, the goal is to grow to as many as 15 lines. The following is a listing of the cell lines available and their originators:

Available Now:

1. JVM2 (Dr. Junia Melo – Royal Marsden Hospital in London, UK)
2. JVM13 (Dr. Junia Melo – Royal Marsden Hospital in London, UK)
3. Mino (Dr. Richard Ford – M.D. Anderson Cancer Center in Houston, TX)

Available October 30, 2007:

4. Z138 (Dr. Zeev Estrov – M.D. Anderson Cancer Center in Houston, TX)
5. REC1 (Drs. Christian Bastard & Elias Campo – Centre Henri Becquerel in Rouen, France)

The MCL Cell Bank was created by the LRF Mantle Cell Lymphoma Consortium and is chaired by Dr. Owen O'Connor of Columbia University. It was made possible by the scientists who generously agreed to share their resources, including Dr. Christian Bastard (Centre Henri Becquerel in Rouen, France), Dr. Elias Campo (University of Barcelona, Spain), Drs. Zeev Estrov and Richard Ford (M.D. Anderson Cancer Center), and Dr. Junia Melo (Royal Marsden Hospital in London, UK).

For more information, visit:
www.mantlecelllymphoma.org

LYMPHOMA

RESEARCH • FOUNDATION

The Lymphoma Research Foundation is pleased to recognize our many generous and compassionate donors for their support of our research, patient education, patient services and advocacy programs.

Thank You!

A special thanks to Millennium Pharmaceuticals for their generous support.

Editor:

Kathleen Brown, MPA, CAE, Director of Research Grant Administration and Professional Programs; Kristofer Prepelica, PhD, Scientific Manager, Research Grants and Initiatives

Writer:

James Testaverde, Research Projects Manager

Consultant:

Marc Hurlbert, PhD, Scientific Director, Science Information Solutions, Inc.

Printing:

Intergraphics Litho Corp.

LRF is MOVING!

As of October 2007, the LRF New York Office will have a new address. See below.

www.lymphoma.org / www.mantlecelllymphoma.org / www.clinfोगroup.org

Los Angeles Office

8800 Venice Boulevard
Suite 207
Los Angeles, CA 90034
310.204.7040 • 800.500.9976
310.204.7043 fax

New York Office

115 Broadway
13th Floor
New York, NY 10006
212.349.2910 • 800.235.6848
212.349.2886 fax