

# LYMPHOMA

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RESEARCH REPORT

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## WHERE ARE THEY NOW? INTERVIEWS WITH PAST GRANTEES

Over the last 15 years, the Lymphoma Research Foundation has awarded over fourteen million dollars in funding to over 200 post-doctoral fellows and career development awardees. How did these grants affect the career paths of these young researchers? Where are they today? How have they continued to fight for better understanding and treatment of lymphoma?

To find out the answers to these questions, LRF spoke to two of our past grantees to see where our grant recipients are now in their careers. Nancy Bartlett, MD, one of our very first recipients, is a prominent clinician and researcher with a leadership role in NIH cooperative group trials. Dean Felsher, MD, PhD runs a research lab at Stanford University.

*Bonus: Recent news in lymphoma research.*

### LRF FELLOWSHIPS, 1992-2007

◆ The Lymphoma Research Foundation (LRF) was formed in November 2001 by the merger of the Cure for Lymphoma Foundation (CFL) and the Lymphoma Research Foundation of America (LRFA). Its mission is to find a cure for lymphoma and serve those touched by the disease. Advocacy, education and assistance for patients are all important to these goals, but at the heart of its mission is its support for lymphoma research.

Every year since 1992, LRF (and LRFA and CFL before it) has solicited research proposals from the best and brightest post-doctoral students nationwide. These proposals are reviewed by the leading lymphoma researchers who make up LRF's Scientific Advisory Board (SAB). The very best and most promising are selected for funding. Funded projects have included a broad spectrum of approaches to the causes and treatments of lymphoma. In this report we follow the careers of two of the talented scientists who have been supported by the foundation.

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### NANCY BARTLETT, M.D. – FELLOW 1992-1994

◆ One of the first recipients of LRF's fellowship award was Nancy L. Bartlett, M.D.. Dr. Bartlett received her award in 1992 for research on the effect of adding G-CSF (granulocyte colony stimulating factor, a growth factor which stimulates production of a type of white blood cell)

to a chemotherapy regimen, to treat intermediate and high-grade non-Hodgkin lymphoma (NHL).

At the time of her award Nancy Bartlett was a postdoctoral researcher at Stanford University. At Stanford, she became keenly interested in the work of Drs. Sandy Horning (a member of LRF's SAB) and Saul Rosenberg (a member emeritus of the SAB), who were



Nancy Bartlett, M.D.

doing groundbreaking clinical research in both Hodgkin and non-Hodgkin lymphoma.

*“Receiving the LRF grant allowed me to add an extra 6 months to my 3-year fellowship. During those last 6 months I was able to cut back on my clinical duties and really focus on learning what it takes to analyze data and prepare a manuscript for publication. I think those 6 months were the most productive of my entire career – I got two papers published in the Journal of Clinical Oncology! I think having that protected time to concentrate on the research was what led me to choose an academic career.”*

Today, Dr. Bartlett is Associate Professor in the Oncology Division of the Department of Medicine at Washington University in St. Louis where she continues her work on developing and conducting clinical trials for patients with NHL and Hodgkin lymphoma. Her current focus is finding new, more effective treatments for patients with relapsed Hodgkin lymphoma, which has a much lower cure rate than primary HL. Dr. Bartlett serves as Hodgkin Lymphoma Cadre leader on the lymphoma committee of Cancer and Leukemia Group B (CALGB), a national cancer cooperative group, and has led or collaborated on a number of CALGB lymphoma trials.

Dr. Bartlett has continued to publish in the field of lymphoma research and has been a participant in the American Society of Hematology and American Society of Clinical Oncology Education Programs. In addition, Dr. Bartlett sits on the editorial board of the Journal of Clinical Oncology.

Despite her busy schedule, Dr. Bartlett makes a point of taking the time to mentor fellows at Washington University. “The other thing about my LRF-sponsored fellowship at Stanford was that it made me see the importance of a good mentor to developing an academic career. It has become a goal of mine to pass on what I learned at Stanford, both in taking care of patients and in doing research.” Several of the fellows Dr. Bartlett has mentored have gone on to pursue successful academic careers in lymphoma clinical research. “That makes me feel it’s been worthwhile,” Dr. Bartlett concluded.

### **DEAN FELSHER, M.D., PH.D - FELLOW, 1996-1998**

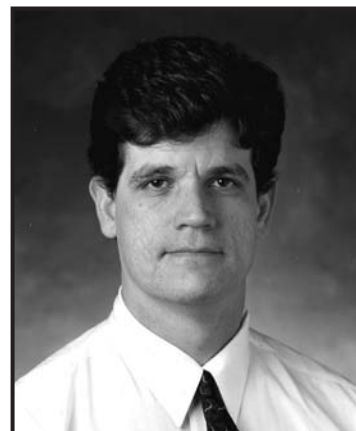
◆ Dr. Dean Felsher earned his M.D. and Ph.D at UCLA, where he worked with pathologist and molecular biologist Jonathan Braun, M.D., Ph.D, currently Chairman of Pathology. Dr. Braun’s work on the role of the immune system in CLL got the young Dr. Felsher, whose grandmother had recently passed away due to lymphoma, interested in this area of research.

In 1996, Dr. Felsher was looking for support for his own, very innovative research project, and was thankful to receive an LRF fellowship.

*“Receiving the grant from LRF, at that time a very small but highly motivated organization, made me feel like it wasn’t just me in my lab, that I was part of a team of people who really cared about this disease”, recalls Dr. Felsher. “Of course, the money made it possible to do the work, but the validation was really precious, too.”*

And as it turned out, Dr. Felsher’s work provided crucial validation for a concept that is now key to a new approach to curing lymphoma and other cancers.

Felsher was the first to demonstrate, by genetically manipulating a mouse to create a “model” of the disease, that reversing a specific genetic defect could reverse the lymphoma.



**Dan Felsher, M.D., Ph.D**

Felsher’s work earned him a faculty appointment at Stanford. He is now an Associate Professor and a member of the Comprehensive Cancer Center. Today, Dr. Felsher runs his own lab with 20 staff.

Dr. Felsher is now working to understand the mechanism behind the reversal effect. Felsher and his team have shown that even though human cancers are the result of multiple genetic changes, the inactivation of a single oncogene, in this case MYC, can induce sustained tumor regression. However after prolonged oncogene inactivation some tumors relapse. These tumors no longer depend on the overexpression of MYC, but acquire novel translocations in their chromosomes. Further work will address the questions of how oncogenes initiate tumorigenesis, how oncogene inactivation causes tumor regression and how tumors escape dependence on oncogenes leading to relapse. Once these mechanisms are fully understood, says Dr. Felsher, oncologists will be able to offer treatment that is specifically tailored to the individual patient’s cancer, and to know ahead of time that it will work, and how it will work. In other words, personalized medicine.

Knowing how important it is to get that initial support for a radically new idea, Dr. Felsher has gone on to mentor other LRF fellows, Dr. Sylvie Giuriato (2003), Dr. Alice Fan (2004) and Dr. Jan van Riggelen (2005). Dr. Giuriato has now herself become an independent scientist and with the help of Dr. Felsher created a mouse model for another type of blood cancer, ALK. “So you’re now funding the next generation of scientific research”, Dr. Felsher stated enthusiastically.

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## NEW IN LYMPHOMA RESEARCH

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### THE PHARMACEUTICAL INDUSTRY

#### DRUGS IN DEVELOPMENT

Many pharmaceutical companies are in the process of designing and testing new cancer drugs, some of which may work for lymphoma. Following are a few recent developments in this area.

◆ Allos Therapeutics started enrolling patients with relapsed or refractory non-Hodgkin or Hodgkin lymphoma in a Phase I/II study of PDX (pralatrexate) and gemcitabine given sequentially, with vitamin B12 and folic acid supplementation. Dr. Steven Horwitz, chair of the study and Assistant Attending Physician at Memorial Sloan-Kettering Cancer Center, New York, said that preclinical findings were “encouraging” and hopes that the study will help researchers better understand PDX’s usefulness as a cancer therapy. <sup>1</sup>

◆ Favril, Inc. announced data from an ongoing Phase II clinical trial of FavId in combination with Rituxan for the treatment of indolent B-cell NHL. Dr. John Hainsworth, principal investigator and chief scientific officer at Sarah Cannon Research Institute, said that “early data show that concurrent treatment with maintenance Rituxan and FavId is feasible and well tolerated.” Investigators are hoping that the combination therapy will enable patients to “experience a longer time to tumor progression beyond what would be expected from Rituxan alone.” The trial is still open to treatment-naïve patients with indolent NHL. <sup>2</sup>

◆ Genitope Corporation announced that it is starting a Phase II clinical trial to evaluate MyVax personalized immunotherapy in patients with previously untreated follicular non-Hodgkin lymphoma. MyVax is also being studied in a Phase III clinical trial. In the Phase II trial, patients will receive rituximab and chemotherapy followed by a series of 24 immunizations with MyVax. Dr. Julie Vose (professor of medicine and chief of Oncology/Hematology at the University of Nebraska Medical Center, and a member of LRF’s SAB) said the initial data suggests that “adding MyVax to the current treatment protocol [for follicular lymphoma] may extend duration of remission while maintaining a well-tolerated safety profile.” <sup>3</sup>

◆ Cell Therapeutics, Inc. announced that the FDA has given fast track designation to pixantrone, a novel anthracenedione (anti-cancer anti-biotic) being developed to treat relapsed or refractory indolent non-Hodgkin lymphoma. In support of its fast track decision, the FDA said that results from phase I and II studies “suggest that

pixantrone is active in this disease” and that the phase III trial being proposed by Cell “has the potential to demonstrate an effect” on refractory indolent NHL. The trial will study pixantrone in combination with fludarabine and rituximab in patients with relapsed or refractory NHL. <sup>4</sup>

### NEWS ON LYMPHOMA RISK AND INDICATORS

#### HIGHER RISK OF NHL FOUND IN OBESE ADULTS

A link between obesity and non-Hodgkin lymphoma was suggested in two recently published studies.

◆ Chiu and colleagues interviewed 387 NHL patients and 535 non-NHL control subjects from 1999 to 2002. For purposes of the study, normal weight was defined as a body mass index (BMI) of 18.5 to 24.9 kg/m<sup>2</sup>. After statistics on weight, height, physical activity, and other lifestyle factors had been collected and analyzed, the investigators found that a higher adult BMI of at least 30.0 was associated with a higher risk of NHL, with the highest risk found in those who had a BMI of 35.0 or higher (a BMI of 30 or over is considered obese). A high BMI in adults aged 40-49 was associated with a higher risk of small lymphocytic, follicular, and diffuse large B-cell lymphoma, as well as NHL overall. <sup>5</sup>

◆ In another study, Larsson and Wolk conducted a meta-analysis of 16 previous studies involving 21,720 cases of NHL. The investigators found a similar link between obesity and NHL, particularly diffuse large B-cell lymphoma. <sup>6</sup>

Please keep in mind that study results like these are rarely the final word. However, as there are now a number of health risks known to be associated with obesity, maintaining a healthy weight is generally advisable.

#### HEPATITIS B AND C INCREASE NHL RISK

◆ Clinical data from two US health systems was used to compare the incidence of NHL in patients with and without chronic hepatitis B virus (HBV) during the period 1995 through 2001. Investigators found that patients having chronic HBV infection were nearly 3 times more likely to develop NHL than those without HBV. <sup>7</sup>

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<sup>1</sup> Allos Therapeutics initiates Phase I/II study of PDX and gemcitabine in patients with non-Hodgkin lymphoma or Hodgkin disease. [press release] *Lab Business Week*, 24 June 2007.

<sup>2</sup> Favril reports status of Phase 2 clinical trial of FavId with maintenance Rituxan for indolent B-Cell non-Hodgkin lymphoma. [press release] *Biotech Business Week*, 18 June 2007.

<sup>3</sup> Genitope Corporation initiates clinical trial to evaluate use of MyVax personalized immunotherapy following treatment with rituximab and chemotherapy for follicular non-Hodgkin lymphoma. [press release] *Lab Business Week*, 10 June 2007.

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<sup>4</sup> Pixantrone granted fast track designation by FDA for relapsed indolent NHL patients. [Cell Therapeutics press release] *Lab Business Week*, 27 May 2007.

<sup>5</sup> Chiu B C-H, Soni L, Gapstur SM et al. Obesity and risk of non-Hodgkin lymphoma (United States). *Cancer Causes Control*. 2007; 18: 677-85.

<sup>6</sup> Larsson SC and Wolk A. Obesity and risk of non-Hodgkins lymphoma: A meta-analysis. *Int J Cancer*. 18 Apr 2007. Available online at [www3.interscience.wiley.com](http://www3.interscience.wiley.com).

<sup>7</sup> Ulcickas-Yood M, Quesenberry CP, Guo D, et al. Incidence of non-Hodgkin lymphoma among individuals with chronic hepatitis B virus infection. *Hepatology*. 24 May 2007. Available online.

◆ In a retrospective study of more than 146,000 patients at US Veterans Affairs health care facilities, investigators found that the hepatitis C virus (HCV) confers a small but significant 20% to 30% higher risk of NHL overall, and a 3-fold higher risk of a low-grade lymphoma known as Waldenstrom macroglobulinemia. This is the largest study to date conducted to assess the risk conferred by HCV for blood cancers. <sup>8</sup>

### STRONGER LINK FOUND BETWEEN NHL AND EPSTEIN-BARR

◆ A retrospective study was conducted by investigators in six European countries to further examine the link between the Epstein-Barr virus (EBV) and lymphoma. They found that the presence of an abnormal reactive anti-EBV antibody increased the risk of B-cell lymphoma, in particular chronic lymphocytic leukemia and extranodal lymphoma. The study confirms earlier findings regarding a link between NHL and Epstein-Barr, but also provides evidence that EBV may be linked to a larger subset of lymphomas than has been previously reported.

### RISK OF LYMPHOMA INCREASED BY FAMILY HISTORY OF CANCER

◆ Using data from the French ESCALE study, investigators determined that a history of cancer in first and second-degree relatives was associated with an increased risk of childhood Hodgkin and non-Hodgkin lymphoma. Odds ratios (a statistical measure of likeliness) were higher when 2 relatives had a history of cancer or when one case of family cancer occurred before the age of 46. The findings support the hypothesis of a familial link to childhood lymphoma, but do not suggest such a link to childhood acute leukemia.

### NHL PROGNOSIS

◆ Researchers at Chonnam National University in Korea recently published fresh data on NHL in their report “Interleukin-10 gene polymorphism influences the

prognosis of T-cell non-Hodgkin lymphomas.” New evidence suggests that the IL-10 gene may be linked to the progression of T-cell NHLs by protecting T cells from programmed cell death. The study looked at the impact of the IL-10 gene on patients’ response to chemotherapy and survival in T-cell NHL, and found a difference in overall survival and failure-free survival related to the presence or absence of this gene polymorphism.

#### Glossary

**FavId:** An anti-idiotypic vaccine. The idiotypic is the specific antigen profile that allows the body to recognize a cell as foreign. Anti-idiotypic vaccines can stimulate the body to produce antibodies against tumor cells.

**Fludarabine:** One of a class of drugs known as purine analogs; it slows or stops the growth of cancer cells.

**Immunotherapy:** Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases.

**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. Also called **transgenic model**.

**Phase I/II:** A trial to study the safety, dosage levels, and response to a new treatment.

**Phase III:** A study to test whether a new treatment has an anticancer effect (for example, whether it shrinks a tumor or improves blood test results) and whether it works against a certain type of cancer.

**Oncogene:** A gene that is capable of causing the transformation of normal cells into cancer cells.

**Rituximab:** A monoclonal antibody used to treat certain types of B-cell non-Hodgkin lymphoma. Monoclonal antibodies are made in the laboratory and can locate and bind to cancer cells. Rituximab binds to the protein called CD20, which is found on B-cells. Also called Rituxan.

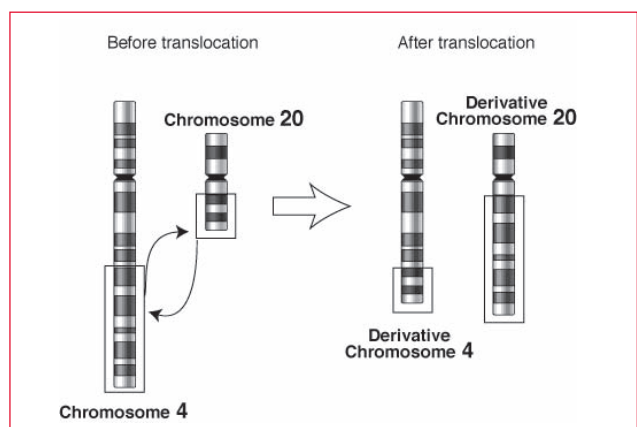
**Translocation:** Breakage and removal of a large segment of DNA from one chromosome, followed by the segment's attachment to a different chromosome.

<sup>8</sup> Giordano TP, Henderson L, Landgren O et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA*. 2007; 297, 18:2010-17.

<sup>9</sup> de Sanjose S, Bosch R, Schouten T, et al. Epstein-Barr virus infection and risk of lymphoma: Immunoblot analysis of antibody responses against EBV-related proteins in a large series of lymphoma subjects and matched controls. *Int J Cancer*. 2007; 7 Jun 2007. Available online at [www3.interscience.wiley.com](http://www3.interscience.wiley.com).

<sup>10</sup> Rudant J, Menegaux F, Leverger G, et al. Family history of cancer in children with acute leukemia, Hodgkin lymphoma or non-Hodgkin lymphoma: the ESCALE study. *Int J Cancer*. 2007; 121 (1), 119-26.

<sup>11</sup> Lee, Je-Jung et al., Interleukin-10 gene polymorphism influences the prognosis of T-cell non-Hodgkin lymphomas. *British Journal of Haematology* 137 (4), 329–336.



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