

Research Report

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A CLOSER LOOK AT LRF'S NEWEST GRANTEES

Research is what makes advances in lymphoma treatment possible. Through research, clinicians and scientists are constantly learning more about cancer and its development and how to combat it. 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.

The Post-Doctoral Fellowships and Clinical Investigator Career Development Awards represent LRF's two cornerstone research programs. These programs have been designed to attract the next generation of young clinicians to the field of lymphoma and support their research training. To date, LRF has awarded 206 Fellowships and 11 Career Development Awards.

In Fall 2007, LRF received 43 applications for these cornerstone research programs. LRF's Scientific Advisory Board, a voluntary group of 45 renowned lymphoma experts, thoroughly reviewed each application and carefully selected the projects and applicants they felt had the greatest potential.

The following researchers represent those most recently selected by LRF. LRF is confident that these young investigators will contribute to the field of lymphoma in invaluable ways, and looks forward to their professional growth and success.

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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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Hudan Liu, MS, PhD
University of Pennsylvania,
Philadelphia, PA

Dr. Hudan Liu received a two-year Post-Doctoral Fellowship to examine the mechanisms behind the abnormal activation of the Notch1 gene and how this influences the development of T-cell acute lymphoblastic leukemia/lymphoma (T-ALL).

While receiving a BS in Biochemistry from Wuhan University in Wuhan, China, Dr. Hudan Liu began her lab training in



Dr. Hudan Liu

molecular biology. After completing her undergraduate degree, Liu earned an MS degree from Shanghai Institute of Biochemistry and Cell Biology in Shanghai, China and a PhD in Cell and Developmental

Biology from Rutgers, State University of New Jersey in Piscataway, NJ.

It was not until Liu joined the Department of Pathology and Laboratory Medicine at the University of Pennsylvania (UPENN), where she is now a Post-Doctoral Researcher, that she became involved in lymphoma research. At UPENN, Liu began studying Notch signaling and how it influences the development of T-cell acute lymphoblastic leukemia/lymphoma (T-ALL).

Liu reports that approximately 60% of T-ALL patients have a Notch1 mutation. Because Notch is responsible for controlling the expression of numerous genes, Liu hopes that by identifying the consequences of a Notch1 mutation she will be able to identify

new signaling pathways and molecules that can be targeted for lymphoma treatment.

To date, Liu and her colleagues have performed specific laboratory techniques on several T-ALL cells and have identified several molecules called mRNAs (molecules similar to DNA that serve as a template for protein production) whose expression is directly controlled by Notch1. Liu is also attempting to identify and characterize microRNAs (small RNAs that are not used as templates for proteins, but regulate gene expression) that are regulated by abnormal Notch signaling.

“Clearly, the identification of activating Notch mutations in T-ALL has revealed a critical target for molecular therapy. My studies will greatly enhance the ability to harness this target for therapeutic benefit,” says Liu.

“It was a great experience to apply for a fellowship from LRF. While writing the proposal, it allowed me to actually sit down and think of my future plans. I am very happy and honored to receive this award since it gives me more freedom in the lab so that I can try something I am really interested in. More excitingly, it offers additional expenses so that I will be able to attend meetings, communicate with peers and receive suggestions and guidance from outside the lab,” says Liu.

Alice Nemajerova, PhD
State University of New York at Stony Brook, Stony Brook, NY

Dr. Alice Nemajerova received a two-year Post-Doctoral Fellowship to investigate the p73 gene and its relationship to the development of lymphoma.

Dr. Alice Nemajerova is a Post-Doctoral



Dr. Alice Nemaierova

Associate in the Department of Pathology at the State University of New York at Stony Brook. She received an MS in Molecular Biology and Genetics as well as a PhD in Cellular and Molecular Biology at Masaryk University in Brno, Czech Republic.

Nemaierova's interest in cancer research was personal and began early. "Both of my parents were diagnosed with this disease many years ago. When selecting a major in college, I did not think twice," says Nemaierova.

"While p53 plays a clear role in tumor suppression, p73 has long eluded efforts to place it in a defined category of cancer biology," says Nemaierova.

Therefore, Nemaierova is investigating whether p73, a gene that is silenced or completely lost in many B-cell lymphomas/leukemias, is an important tumor suppressor and DNA stability factor in B-cell lymphomas. She hypothesizes that B-cells deficient in p73 are prone to DNA damage and rearrangements, resulting in the development of lymphoma. If this hypothesis holds true, p73 and its molecular mechanisms could be used as a target for therapy or as a way to predict prognosis and response to therapy.

With the funding she received from the Lymphoma Research Foundation, Nemaierova will begin studying the p73 gene in mice. "My approach is based on mouse models of human disease and will allow me

to gain mechanistic insight into the function of tumor suppressors, such as p53 and p73, and tumor prevention," says Nemaierova. "This grant ensures that I will be able to employ the most up-to-date methods and techniques for a large-scale analysis of p73 function."

When asked about the importance of the Lymphoma Research Foundation's Post-Doctoral Fellowship, Nemaierova went on to say, "I regard this grant as a unique opportunity to expand my knowledge, expertise, and understanding of the molecular mechanisms of cancer. It will help me participate in scientific conferences and to extend my collaboration with other laboratories working in the field. This grant will help me become an independent researcher; preparing me for a future career in academia or within a medical institution."

Dr. Patrick Ng received a two-year Post-Doctoral Fellowship to develop fusion protein therapeutics that will direct the immune system to attack cancer cells.

Patrick Ng, PhD
Stanford University Medical School,
Stanford, CA

Dr. Patrick Ng started his research career as an undergraduate studying molecular biology at the University of California, Berkeley. While attaining his BA, Ng participated in several laboratory research projects and a summer internship at a pharmaceutical



Dr. Patrick Ng

an undergraduate studying molecular biology at the University of California, Berkeley. While attaining his BA, Ng participated in several laboratory research projects and a summer internship at a pharmaceutical

company. After college, Ng earned a PhD in Immunology from the University of California, Los Angeles. As a graduate student, Ng studied the biological effects of fusion proteins (protein products of different genes fused together by DNA engineering).

Because of his background in fusion protein construction and characterization, he joined the laboratory of Ronald Levy, MD, (current member of the Lymphoma Research Foundation's Scientific Advisory Board) at Stanford University, to assist in the development of a cancer vaccine for B-cell lymphomas. The ultimate goal of the project is to isolate a patient's own tumor cells to develop a custom made fusion protein vaccine that, when injected back into the patient, will "educate" the immune system to mount a natural attack against the cancer, while sparing normal tissues.

According to Ng, it takes approximately 6-9 months per patient to generate a personalized vaccine with current methods. Using a novel E. coli extract-based protein synthesis system developed by James Swartz, PhD, (Chemical Engineering Department, Stanford University) Ng showed that it is possible to generate a personalized vaccine in a few weeks. This system of vaccine production is more cost-effective and it shortens the time from diagnosis to treatment.

With the funding he received from the Lymphoma Research Foundation, Ng will continue to develop two classes of fusion protein vaccines for the treatment of B-cell lymphomas. To date, Ng and his colleagues have shown that both types of vaccines can induce strong cancer-specific immune responses in animal models.

"Many B-cell lymphomas are incurable with treatments available today. Alternative therapeutic strategies with low toxicity are urgently needed. I believe patient-specific fusion protein vaccines are a very promising

approach, and the support from LRF is crucial to its development," says Ng.

Steven Park, MD Fred Hutchinson Cancer Research Center, Seattle, WA

Dr. Steven Park received a two-year Post-Doctoral Fellowship to optimize radioimmunotherapy by reducing toxicity.



Dr. Steven Park

Dr. Steven Park started his research career in a biomechanics laboratory while earning a BA in Integrative Biology from the University of California, Berkeley. His interest in leukemia and

lymphoma developed during medical school at the University of California, Davis where he received a one year grant from the American Cancer Society to study a peptide that targets lymphoma cells.

After graduating medical school, Park became a resident physician at the University of Washington Medical Center in Seattle, WA and began working on a T-cell immunotherapy project with Oliver Press, MD, PhD (immediate past chairman of Lymphoma Research Foundation's Scientific Advisory Board and Chairman of the Follicular Lymphoma Consortium). Park chose to remain at the University of Washington Medical Center and Fred Hutchinson Cancer Research Center where he is now a Clinical Research Fellow.

With funding he received from the Lymphoma Research Foundation, Park is

discovering ways to optimize the radioimmunotherapy (RIT) technique while minimizing radiation exposure, or toxicity, to normal cells.

Conventional RIT utilizes an antibody directly attached to a radioactive material that, when injected into the body, specifically targets cancer cells delivering a lethal dose of radiation. This method is beneficial because it minimizes radiation exposure to other organs. However, with conventional RIT, the disease often comes back. One method used by scientists to prevent lymphoma from coming back after RIT is to give very high doses of radiation with a bone marrow transplant. However, according to Park, "There can be serious toxicities associated with high dose radiation and bone marrow transplant."

To further minimize radiation exposure to normal organs and bone marrow, thereby making a bone marrow transplant unnecessary, Park and his colleagues have been testing a new RIT method called pre-targeted radioimmunotherapy. This method takes advantage of the incredibly strong interaction between streptavidin (a protein) and biotin (a vitamin).

"In conventional RIT, the toxicity mainly comes from the antibody circulating in the body for an extended period of time," says Park. "What we do with the pre-targeted therapy is separate the antibody from the radioisotope. First, we inject antibody bound to streptavidin and allow enough time for the antibody to localize at the tumor site. Then, we inject a clearing agent that basically clears any unbound antibody into the liver. After clearance, biotin bound to a radioisotope is injected. The biotin-radioisotope then seeks out and binds to the antibody-streptavidin complex on the tumor. Since biotin is very small it gets cleared from the body very quickly, within minutes to hours." According to Park, one caveat of the system is

that humans normally have biotin circulating in their bloodstream. This naturally present biotin can block the binding site of streptavidin, thereby impairing the binding of the biotin-radioisotope complex. In order to overcome this problem, Pat Stayton, PhD, at the University of Washington, has created a modified streptavidin that does not bind to naturally occurring biotin, but instead, has a high binding capacity to a synthetic biotin.

Park is now testing the therapeutic effects of this modified streptavidin in animal models. He hopes that this novel treatment method will provide a cure for patients with lymphomas without the toxicities associated with bone marrow transplant.

Christian Steidl, MD
British Columbia Cancer Agency,
Vancouver, Canada

Dr. Christian Steidl received a two-year Post-Doctoral Fellowship to help identify Hodgkin lymphoma patients that are unlikely to succeed with standard therapy through genetic analysis.

After completing a medical degree and PhD in



Dr. Christian Steidl

Germany, Dr. Christian Steidl became a Resident/Physician Scientist at Georg-August Universitaet in Goettingen, Germany where he specialized in internal medicine with a focus on hematology. After four years, he

received funding from the German Research Foundation to conduct research at the British

Columbia Cancer Agency in Vancouver, Canada where he is currently a Pathology Research Fellow working with Randy Gascoyne, MD, FRCPC (a member of the Lymphoma Research Foundation's Scientific Advisory Board and MCL Lymphoma Consortium).

Steidl's interest in lymphoma started during his medical training. "When I started my residency in internal medicine, I chose to specialize in hematology because, from a clinical perspective, I wanted to help patients affected by blood cancers. From a research perspective, hematological cancers are a good model to study," says Steidl.

According to Steidl, approximately 20% of Hodgkin patients fail standard therapy. As a result, Steidl has set out to find a way to predict how a person will or will not respond to therapy by looking at their genetics. With the funding he has received from the Lymphoma Research Foundation (LRF), he will be examining purified malignant and non-malignant cells from Hodgkin-affected lymph node tissues through a variety of high-resolution genetic analyses. He will then correlate the findings with treatment outcomes in a large number of cases. The results will help identify patients unlikely to succeed with standard therapy and make them candidates for innovative, alternative treatment options.

"It would be beneficial to find these people upfront. Current clinical parameters are very imprecise," says Steidl. "Identifying these predictive factors would have a big impact."

Steidl's project was also recognized by the Cancer Research Society. LRF is pleased to join with them to help Steidl conduct his research. Steidl feels these funding opportunities are an integral part of his education and are necessary for him to move forward in his research career.

"Financially, I am dependent on these grants

right now because I am responsible for securing my own funding. These will be the final two to three years before I can apply for a faculty position in North America or go back into the European system and have my own lab. This funding is crucial for me in order to achieve my goal to become an independent researcher" says Steidl.

Jing Yang, MS, PhD
MD Anderson Cancer Center,
Houston, TX

Dr. Jing Yang received a two-year Post-Doctoral Fellowship to study novel antibodies capable of killing mantle cell lymphoma cells and improve their effectiveness.



Dr. Jing Yang

Dr. Jing Yang is a Post-Doctoral Fellow in the Division of Cancer Medicine at the MD Anderson Cancer Center in Houston, TX. She received a PhD in Molecular Biology from Xiangya Medical School, Central South

University in Changsha, China where she studied nasopharyngeal carcinoma.

At MD Anderson Cancer Center, Yang and her colleagues have recently developed novel monoclonal antibodies (mAbs) that specifically target human $\beta 2$ -microglobulin ($\beta 2M$), a small protein normally found on the surface of many cells, including lymphocytes. Elevated levels of $\beta 2M$ can be found in mantle cell lymphoma (MCL) patients and are correlated with a poor patient outcome. "These results point to an important yet unidentified role of $\beta 2M$ in MCL. Thus, targeting or blocking $\beta 2M$ with specific

antibodies may alter these effects and slow disease progression,” says Yang.

With funding from the Lymphoma Research Foundation, Yang will begin testing the anti- β 2M antibodies against MCL in human-like mouse models to see if the therapy is effective. Yang will also be investigating the specific mechanisms by which these antibodies cause cancer cell death.

Another aim of her study is to determine whether combining the anti- β 2M antibodies with other chemotherapy drugs, such as rituximab (Rituxan) or bortezomib (Velcade), has an added therapeutic advantage.

Yang hopes that further characterization of the antibodies and their effects will provide the necessary evidence for future clinical application. “I became interested in this project because this antibody has a lot of potential for the treatment of lymphoma. I think that it will be available as a therapy in the future,” says Yang.

Yang became very excited when asked what this funding will allow her to do. “This money is very important for me and my future career because I am a junior investigator and I need a lot of training. It will help me grow and develop into an independent investigator,” says Yang

Brian Till, MD
Fred Hutchinson Cancer Research
Center, Seattle, WA

Dr. Brian Till received a three-year Clinical Investigator Career Development Award to test a new treatment for non-Hodgkin lymphoma and improve its effectiveness.

Dr. Brian Till became interested in research

while attending college at Catholic University in Washington, DC. Before finishing his BS degree, he completed three cancer-related



Dr. Brian Till

research internships. He continued conducting research between his first and second year of medical school at the University of Chicago where he studied chromosomal abnormalities in cancer.

During his internal medicine residency at the University of Pennsylvania, he became progressively more interested in cancer research, and he collaborated with Stephen Schuster, MD, to conduct a retrospective study comparing tositumomab and iodine I 131 tositumomab (Bexxar) with ibritumomab tiuxetan (Zevalin) to determine whether patients with relapsed non-Hodgkin lymphoma responded better to one or the other. “Although I was not able to finish the project by the time that I left, it was my first taste of clinical research and it was very interesting,” says Till.

In 2005, Till began an oncology fellowship at the Fred Hutchinson Cancer Research Center in Seattle, WA where he is now a Senior Fellow. It was here that he began working with Oliver Press, MD, PhD, (immediate past chairman of Lymphoma Research Foundation’s Scientific Advisory Board and Chairman of the Follicular Lymphoma Consortium) to test a new treatment for non-Hodgkin lymphoma which involves genetically engineering a patient’s T-cells to help them recognize and kill lymphoma cells. “We are interested in finding new therapies for incurable types of lymphoma that are much safer and less toxic than current stem

cell transplantation,” says Till.

Till and his colleagues recently completed a phase I trial of a technique pioneered by Michael Jensen, MD, at the City of Hope National Medical Center in California, to treat patients with relapsed/refractory indolent lymphoma and mantle cell lymphoma. The first step of the procedure involves extracting a person’s T-cells. The T-cells are then genetically engineered to express a receptor that targets the surface of lymphoma cells (specifically, the cell surface antigen CD20). After the T-cells are grown in the laboratory, they are infused back into the patient in a series of three T-cell infusions, which takes place over about one week. Following the last infusion, patients are injected with a special compound (interleukin-2, also known as IL-2) designed to extend the length of time that the T-cells can survive in the body. Patients continue to give themselves injections of IL-2 twice a day for two weeks. Once in the body, the T-cells move throughout the bloodstream and attach themselves to the tumor cells, which hopefully results in an immune response that destroys the cancer.

The results of this study were promising in that the treatment was safe and well-tolerated by the patients, but the clinical responses were not as favorable as Till anticipated. Therefore, with the funding he received from the Lymphoma Research Foundation, Till intends to conduct a second clinical trial which will test whether enhancing the modified T-cells with two co-stimulatory domains creates a more effective response. “Our primary goal is to assess the safety, toxicity, and feasibility of this therapy. A secondary aim is to look for clinical responses,” says Till. He remains hopeful that this therapy will be an effective strategy for the treatment of relapsed mantle cell lymphoma and indolent non-Hodgkin lymphoma.

Finding research funding as a young investigator is often difficult, explained Till. “Funding is important for young investigators because it is very difficult to get a big grant while you are a fellow. It really takes a few years to become proficient with research techniques, obtain data, and publish. Most institutions will not keep you around for free after your fellowship; you need to pay your own way with grant funding. This three year grant gives me time and will put me on track to being an independent investigator,” says Till.

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