Spring/Summer 2010
Volume 4, Issue 3

University of Iowa Holden Comprehensive Cancer Center
University of Iowa Health Care
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Mayo Clinic Cancer Center

SPORE

THE UNIVERSITY OF IOWA / MAYO CLINIC **S**PECIALIZED **P**ROGRAM **O**F **R**ESEARCH **E**XCELLENCE

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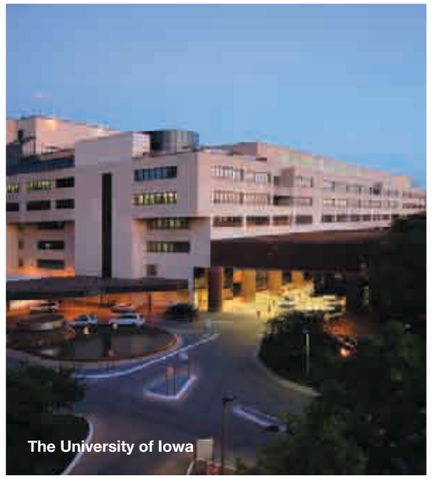
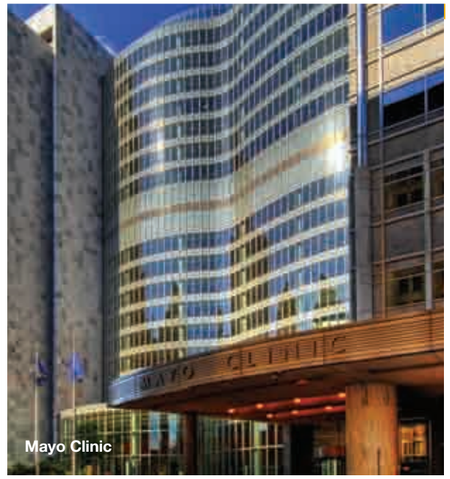

The University of Iowa


Mayo Clinic

The primary goal of The University of Iowa/ Mayo Clinic Specialized Program of Research Excellence (SPORE) Program is to apply scientific advances to the development of new approaches to the prevention, detection and therapy of lymphoma and lymphoid leukemias. The SPORE program is composed of scientists and physicians from the University of Iowa and Mayo Clinic with an interest in both research and the clinical care of patients with these disorders.

The SPORE has been supported since 2002 by a grant from the National Cancer Institute. SPORE progress and plans were reviewed in 2007 by a group of cancer experts from around the country who gave the program a rating of "outstanding". Based on this review, SPORE funding from the NCI was renewed for an additional five years. This renewal will allow us to continue our most promising research programs, and more importantly, our development of new approaches to treatment of these cancers.

This newsletter outlines some of the progress that we have made through SPORE research including research that was presented in December of 2009 at the American Society of Hematology Meeting - a Forum where experts from around the world exchange research information and meet to discuss new approaches to detection and treatment of blood related cancers.

We are deeply indebted to the many patients who agreed to participate in research studies and have made this progress possible, and to the many volunteers and researchers who have contributed so much to the success of these programs. We look forward to keeping you informed about the results of our research as we continue to make progress against lymphoma and related diseases.

With warmest regards,

George J. Weiner, M.D. and Thomas E. Witzig, M.D.,
on behalf of The University of Iowa/ Mayo Clinic Lymphoma SPORE Researchers

RESEARCH SUPPORT

If you would like to be a part of our future and support the leukemia and lymphoma research being done through the Lymphoma SPORE, please contact Tori Erickson at (319) 335-3305, or donations may be sent to the University of Iowa Foundation, PO Box 4550, Iowa City, IA 52244-4550. Please indicate your gift is to support the Iowa/Mayo Lymphoma SPORE program.

For comments or more information, please write to us at:

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Iowa City, IA 52242

Lymphoma/Leukemia Study
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Rochester, MN 55905

SPORE Researchers Present Results at Major Meeting

Held annually in December, the American Society of Hematology's annual meeting provides hematologists from around the world a forum for discussing critical issues in hematology. More than 21,000 clinicians, scientists, and others attend the four-day meeting, which consists of a superb educational program and cutting-edge scientific sessions. The annual meeting features oral and poster presentations that are chosen by peer-reviewers from abstracts submitted prior to the meeting and contain the latest and most exciting developments in scientific research. Plenary symposia and named lectures on specialized areas of hematology are also presented throughout the meeting program.

The following abstracts related to the SPORE were selected for presentation at this year's ASH meeting.

A Phase II Study of Temsirolimus (CCI-779) in Combination with Rituximab in Patients with Relapsed or Refractory Mantle Cell Lymphoma
Ansell, SM, Tang, H, Kurtin, P, Koenig, P, Inwards, DJ, Shah, K, and Witzig, TEA Phase II Study of Temsirolimus (CCI-779) in Combination with Rituximab in Patients with Relapsed or Refractory Mantle Cell Lymphoma

Inhibition of the Jak/Stat Pathway Downregulates Immunoglobulin Production and Induces Cell Death in Waldenstrom Macroglobulinemia
Ansell, SM, Grote, D, Elsawa, SF, Gupta, M, Ziesmer, SC, Novak, AJ, and Witzig, TEInhibition of the Jak/Stat Pathway Downregulates Immunoglobulin Production and Induces Cell Death in Waldenstrom Macroglobulinemia

Deficiency of MnSOD in Hematopoietic Stem Cells Causes a Sideroblastic Anemia-Like Phenotype
Case, AJ, Wagner, BA, Buettner, GR, and Domann, FEDeficiency of MnSOD in Hematopoietic Stem Cells Causes a Sideroblastic Anemia-Like Phenotype

Heightened Susceptibility to Influenza Mortality in Immunodeficient Mice Caused by a T-Cell Specific Defect in SOD2
Case, AJ, Mcgill, JL, Sangster, SC, Madsen, JM, Tygrett, LT, Johns, AG, Takahashi, T, Shirasawa, T, Spitz, DR, Meyerholz, DK, Waldschmidt, TJ, Legge, KL, and Domann, FEHeightened Susceptibility to Influenza Mortality in Immunodeficient Mice Caused by a T-Cell Specific Defect in SOD2

Germline Variation in Complement Genes and Event-Free Survival in Follicular Lymphoma
Cerhan, JR, Maurer, MJ, Novak, AJ, Ansell, SM, Macon, WR, Slager, SL, Weiner, GJ, Witzig, TE, and Habermann, TMGermline Variation in Complement Genes and Event-Free Survival in Follicular Lymphoma

MYC Translocations Are Associated with Poor Overall Survival in DLBCL Patients in Both the Chemotherapy and Immunochemotherapy Eras
Dogan, A, Maurer, MJ, Macon, WR, Inwards, DJ, Micallef, IN, Johnston, PL, Law, M, Ristow, K, Witzig, TE, Cerhan, JR, and Habermann, TMMYC Translocations Are Associated with Poor Overall Survival in DLBCL Patients in Both the Chemotherapy and Immunochemotherapy Eras

Vitamin D Deficiency Is Associated with Inferior Event-Free and Overall Survival in Diffuse Large B-Cell Lymphoma
Drake, MT, Maurer, MJ, Link, BK, Micallef, IN, Habermann, TM, Kelly, JL, Macon, WR, Nikcevich, D, Colgan, JP, Allmer, C, Slager, SL, Weiner, GJ, Witzig, TE, and Cerhan, JRVitamin D Deficiency Is Associated with Inferior Event-Free and Overall Survival in Diffuse Large B-Cell Lymphoma

Granzyme B Produced by Human Plasmacytoid Dendritic Cells Suppresses T Cell Expansion
Fabricius, D, Vollmer, A, Blackwell, S, Maier, J, Sontheimer, K, Beyer, T, Mandel, B, Lunov, O, Tron, K, Nienhaus, GU, Simmet, T, Debatin, K-M, Weiner, GJ, and Jahrsdoerfer, BGranzyme B Produced by Human Plasmacytoid Dendritic Cells Suppresses T Cell Expansion

Evaluating the Antitumor Activity of MLN9708 in a Disseminated Mouse Model of Double Transgenic iMyc Ca/Bcl-XL Plasma Cell Malignancy
Fitzgerald, M, Cao, Y, Bannerman, B, Li, Z, Tayber, O, Li, P, Terkelsen, J, Bradley, D, Frazer, J, Silverman, L, Janz, S, Van Ness, BG, Kupperman, E, Manfredi, M, and Lee, EEvaluating the Antitumor Activity of MLN9708 in a Disseminated Mouse Model of Double Transgenic iMyc Ca/Bcl-XL Plasma Cell Malignancy

Stimulation of B-CLL Cells with Interleukin 21 and Toll Like Receptor Agonists Induces a CTL-Like Transcriptional Profile
Hagn, M, Ebel, V, Sontheimer, K, Beyer, T, Blackwell, SE, Simmet, T, Weiner, GJ, and Jahrsdoerfer, BStimulation of B-CLL Cells with Interleukin 21 and Toll Like Receptor Agonists Induces a CTL-Like Transcriptional Profile

The Novel Proteasome Inhibitor MLN9708 Demonstrates Efficacy in a Genetically-Engineered Mouse Model of DeNovo Plasma Cell Malignancy
Janz, S, Van Ness, BG, Neppalli, V, Liu, R, Pickard, MD, Terkelsen, J, Bradley, D, Hu, L, Kupperman, E, Manfredi, M, and Lee, EThe Novel Proteasome Inhibitor MLN9708 Demonstrates Efficacy in a Genetically-Engineered Mouse Model of DeNovo Plasma Cell Malignancy

MLN9708 Elicits Pharmacodynamic Response in the Bone Marrow Compartment and Has Strong Antitumor Activity in a Preclinical Intraosseous Model of Plasma Cell Malignancy
Lee, E, Bannerman, B, Fitzgerald, M, Terkelsen, J, Bradley, D, Li, Z, Li, P, Janz, S, Van Ness, BG, Manfredi, M, and Kupperman, EMLN9708 Elicits Pharmacodynamic Response in the Bone Marrow Compartment and Has Strong Antitumor Activity in a Preclinical Intraosseous Model of Plasma Cell Malignancy

Elevated Pre-Treatment Serum Immunoglobulin Free Light Chains (FLC) Are Associated with Poor Event-Free and Overall Survival in Diffuse Large B-Cell Lymphoma (DLBCL)
Maurer, MJ, Micallef, IN, Katzmann, JA, Nikcevich, D, and Witzig, TEElevated Pre-Treatment Serum Immunoglobulin Free Light Chains (FLC) Are Associated with Poor Event-Free and Overall Survival in Diffuse Large B-Cell Lymphoma (DLBCL)

Elevated Expression of GPR34 in Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma and Its Association with Increased Cell Growth, Erk Activation, and AP-1 and CRE-Mediated Transcription
Novak, AJ, Akasaka, T, Manske, M, Price-Troska, T, Gupta, M, Witzig, TE, Dyer, MJ, Dogan, A, and Ansell, SMElevated Expression of GPR34 in Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma and Its Association with Increased Cell Growth, Erk Activation, and AP-1 and CRE-Mediated Transcription

GA101-Coated Target Cells Are More Effective Than Rituximab-Coated Target Cells at Activating NK Cells When Complement Is Present
Spaunhorst, B and Weiner, GJGA101-Coated Target Cells Are More Effective Than Rituximab-Coated Target Cells at Activating NK Cells When Complement Is Present

Rituximab Infusion Induces NK Activation in Subjects with the High Affinity CD16 Polymorphism
Weiner, GJ, Veeramani, S, Wang, S-Y, Dahle, C, Blackwell, S, Jacobus, L, Knutson, T, Knutson, AC, Smith, BJ, and Link, BKRituximab Infusion Induces NK Activation in Subjects with the High Affinity CD16 Polymorphism

Durable Responses After Lenalidomide Oral Monotherapy in Patients with Relapsed or Refractory (R/R) Aggressive Non-Hodgkin's Lymphoma
(a-NHL): Results From An International Phase 2 Study (CC-5013-NHL-003)
Witzig, TE, Vose, JM, Zinzani, PL, Reeder, CB, Buckstein, R, Polikoff, J, Guo, P, Pietronigro, D, Ervin-Haynes, A, and Czuczman, MSDurable Responses After Lenalidomide Oral Monotherapy in Patients with Relapsed or Refractory (R/R) Aggressive Non-Hodgkin's Lymphoma (a-NHL): Results From An International Phase 2 Study (CC-5013-NHL-003)

Elevated Serum sIL-2Ra Levels Facilitate IL-2 Signaling and Contribute to Impaired Tumor Immunity in B-Cell Non-Hodgkin Lymphoma (NHL)
Yang, Z-Z, Ziesmer, SC, Novak, AJ, Witzig, TE, and Ansell, SMElevated Serum sIL-2Ra Levels Facilitate IL-2 Signaling and Contribute to Impaired Tumor Immunity in B-Cell Non-Hodgkin Lymphoma (NHL)

PROFILE

Paying it Forward

By Delila Kern

Delila Kern
Graduate Student
The University of Iowa

I was born and raised in Canada. As an only child to my parents, I had to learn how to keep myself occupied so I immersed myself in books. Around age 12 I became fascinated with my mother's medical anatomy book. It was then that my love for the medical sciences began. I would read pages of medical information and study the pictures of various medical conditions. I excelled in science, won awards in high school, and eventually went on to earn my bachelors degree in Genetics, Cell Biology and Development.

When I was diagnosed with lymphoma in July of 2007 it was quite a shock. I was 26 years old and was pursing my master's degree in Neurobiology. At the time I knew little about lymphoma, but as do many, I began to research as much information as I could about it. Having a scientific background made it slightly easier for me to understand all the scientific jargon, so I read all the scientific articles that I could and asked my oncologist hundreds of questions. I became more informed about lymphoma.

Going through various chemotherapies, radiation treatments and a bone marrow transplant was extremely difficult. I spent weeks in the hospital and went through some very dark days in the isolation unit. Little by little, I began to recover and feel better. I had a lot of time to think when I was in the hospital, and it was from that point on that I decided that I wanted to do cancer research.

In August of 2009 I began my Ph.D. studies at the University of Iowa in the Biosciences program. I sought out Dr. George Weiner, and was thrilled to have the opportunity to do a rotation in his laboratory. I was able to research something that is very close to my heart and I am tremendously grateful to the lymphoma team for allowing me the opportunity to learn and partake in an amazing research project. I was also able to participate in SPORE conferences and the SPORE retreat, and interact with outstanding lymphoma researchers from both Iowa and the Mayo Clinic. Currently I am rotating in Dr. Apollina Goel's research lab, who also does research on lymphoma and multiple myeloma. Dr. Goel received her research training at the Mayo Clinic and is now an Assistant Professor at the University of Iowa further highlighting the value of the strong interactions between these two great institutions.

Being part of the SPORE team has allowed me to grow as a student and has given me the foundation to become a great researcher. Their team of doctors, scientists, and students are working hard at finding a cure for lymphoma. How do I know this? I am one of them. If I can help in the fight against cancer, even if just a little, I will feel like I have paid it forward.

NHL/CLL Family Study Summary

Thank you to all who have participated in the NHL/CLL family study. We are humbled by your sacrifice of time and energy in providing critical information for our study. This effort has not been in vain as valuable findings from the family study are now coming to fruition after years of work. To date, 788 individuals from 215 families have participated in our study. If we include results from our collaborating recruitment sites across the United States, we have over 350 families. Our sites include Duke University, M.D. Anderson Cancer Center, Mayo Clinic, National Cancer Institute, University of Iowa, University of Utah, and University of California, San Diego.

In the past year, our study has had exciting breakthroughs in the search for genetic links responsible for increasing risk of CLL. Results from this project helped to identify and validate 6 genetic variations that CLL patients have more often than individuals without CLL. Similar findings were initially reported by a European study group in 2008. Together, these results establish that CLL has a series of confirmed genetic variations that increases one's risk of getting CLL. It is important to note that the genetic variations identified have only been found to increase one's risk of disease; they do not actually cause an individual to get the disease. Therefore, at this point, we do not recommend that an individual get tested for these genetic variants. The next stage of research is to understand the role of these genetic variations with CLL risk; e.g., why do these genetic variations increase the risk of CLL? We are also continuing to search for additional genetic variations.

We have new developments emerging from our study. Monoclonal B-cell lymphocytosis, or MBL, is a benign condition that is virtually unknown outside the field of hematology. However, initial research is showing that MBL may be closely linked with the development of lymphoma. Of importance to our study, MBL is most often found in people with a family history of CLL. For instance, while MBL naturally occurs in around 3% of the general population, our research has shown that MBL occurs in up to 17% of individuals with a family history of CLL. It has been hypothesized that MBL may be a precursor to CLL, meaning that individuals who are diagnosed with CLL may have had MBL prior to their CLL diagnosis. Important information to note is that MBL is somewhat common, and not everyone who has MBL goes on to have CLL. Further, emerging data from our study suggest that MBL is occurring in people with a family history of NHL. More research is needed to better understand the significance of these findings and understand which individuals with MBL are most likely to progress to have CLL or NHL. Our study group is working to aid in this research.

Please feel free to contact us with any questions that you may have regarding this study by calling:

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Top to Bottom, left to right
Row 1: Paloma Giangrande, Mamta Gupta, Anne Novak, Zuhair Ballas, George Weiner, Matthew Drake, Tom Witzig
Row 2: Usha Perepu, Allison Knutson, Brian Smith, Andrew Feldman, Tina Knutson
Row 3: Zhi Zhang Yang, Julianne Lunde, Olga Richter, Delila Kern
Row 4: Laura Sturz, John Janczy, Sara Bonde, Amy Eisenberg, Suresh Veeramani, Andrea Park
Row 5: Ken Saling, Stephen Ansell, Lorraine Dorfman, Sue Blackwell, Allan Dietz
Row 6: Tom Griffith, Susan Slager, Brian Link, Nancy Ray
Row 7: Grzegorz Nowakowski, Clive Zent, Betsy Chrischilles, Jim Cerhan, Chris Dahle
Row 8: Terry Braun, Ben Haines, Siegfried Janz, Laura Jacobus

Meet Our Investigators

George J. Weiner, M.D.
University of Iowa
Holden Comprehensive Cancer Center

It is hard for George Weiner to believe he has been at the University of Iowa for over 20 years. When he moved to Iowa City with his wife Teresa, his children were 3 years, 1 ½ years and 6 weeks old respectively. His youngest is now a Junior in college. Much has changed during those 20 years. When Dr. Weiner began his research on anti-lymphoma antibodies, many experts questioned whether they would ever be useful. Now they are a mainstay of therapy, and through work done by many researchers including those in the SPORE, they continue to help more and more patients. Dr. Weiner initially spent his time at work in the research laboratory and seeing patients. He never envisioned himself in a role as an administrator. What he enjoys most about the time he spends in administration now is working with outstanding people who have different backgrounds and areas of expertise, but a shared vision and purpose. "I would never want to give up my own research, but helping lead the Iowa/Mayo Lymphoma SPORE is very fulfilling. The collaborative approach taken by Tom Witzig and his team at Mayo, and my colleagues here at Iowa, has allowed us to accomplish so much more than any of us could have done alone. We are all working together towards the goal of helping patients with lymphoma and leukemia. It is very rewarding to see progress in research we helped support, even if it did not take place in my own research laboratory." In his spare time, Dr. Weiner enjoys spending time with his family, an occasional scuba dive when traveling, photography, jogging and biking. If you happen to live near the route for RAGBRAI (the Register's Annual Great Bike Ride Across Iowa) this summer, drop him a line. He will be among the thousands of other bikers pedaling their way across Iowa, and would love to stop by and say hello.

Thomas E. Witzig, M.D.
Mayo Clinic Cancer Center

Dr. Thomas E. Witzig Thomas Witzig is the other half of the University of Iowa/Mayo Clinic Lymphoma SPORE Administrative team. He grew up in central Illinois and became interested in Hematology when he was an internal medicine resident at the University of Iowa. It was there, under the tutelage of Dr. Henry Hamilton and Dr. James Armitage that he decided to do a fellowship in hematology/oncology. At the Mayo Clinic in Rochester Minnesota he developed an interest in B-cell malignancies and since 1986 has been performing translational research and clinical trials in lymphoma and related cancers. "Working with Dr. Weiner over the last eight years has been a real pleasure. I believe that the two of us working together along with the teams at the University of Iowa and the Mayo Clinic have been able to produce more research more rapidly than either group could have done by themselves. We each bring unique strengths to the job and in the end the patients are the winners." Dr. Witzig spends a substantial amount of time working with patients on clinical trials. "The most fun that a physician scientist ever experiences is to see a patient get better in response to a new treatment modality. That really makes my day and spurs me on," says Dr. Witzig. In his spare time Dr. Witzig also enjoys biking but not to the level of Dr. Weiner! He is also a hobby beekeeper and he and his wife put out a "limited edition" (limited by volume) honey product each year. Dr. Witzig and his wife Diane have two children: Erin who is a teacher in Minneapolis and Ryan who is a junior at the Air Force Academy.

LYMPHOMA PATIENT ADVOCATE SUPPORT PROGRAM

The patient advocates are associated with the Lymphoma SPORE as volunteers. They are a resource that any patient or family member can utilize, and they can enjoy hearing from you and helping out as they are able. If you would like more information about the patient advocate in your area you may contact the Cancer Information Center at the University of Iowa, **800-237-1225** or Julianne Lunde at the Mayo Clinic, **800-610-7093**.

The UI/MC SPORE consists of research projects, core resources, and the Career Development and Developmental Research Programs. Specific projects are as follows:

- A Novel Approach to the Immunotherapy of B-cell Malignancies
- Signal Transduction Inhibitor Therapy for Lymphoma
- Biology and Epidemiology of APRIL and BLyS in B-cell NHL
- Targeted Therapy Exploiting the Malignant B-cell Microenvironment Interface
- Monoclonal Antibody Induced NK Cell Activation & Complement
- TH17 and Regulatory T-Cell Interactions in B-Cell Non-Hodgkin Lymphoma

Core resources include Administration, Biostatistics and Bioinformatics, Biospecimens, and Clinical Research that supports both clinical trials and the Molecular Epidemiology Resource of the UI/MC SPORE. All units within the UI/MC SPORE work to draw on the resources of both institutions to expedite the translation of discoveries into new and better approaches to the prevention and treatment of lymphoma.

A Novel Approach to the Immunotherapy of B-cell Malignancies

This project is making progress with respect to both clinical trials and basic laboratory research. The clinical trial for this project involves treatment of patients with chronic lymphocytic leukemia, with CpG oligonucleotides, an immunostimulatory agent that is known in the test tube to induce death of CLL cells. The ongoing study is designed to explore the effects of a single dose of CpG ODN in patients with CLL and to evaluate how the amount of CpG and route of administration impacts on its effects. This portion of the study has now been completed and the trial has moved on to where individual patients are receiving multiple doses. This effort has been led by Dr. Clive Zent. In addition, the laboratory of Dr. George Weiner is exploring how CpG ODN and other agents impact on both CLL cells and on cells involved in development of immune response known as dendritic cells. Weiner and colleagues have made the unexpected observation that the lymphocytes and dendritic cells can produce a protein called granzyme B that was not previously known to be made in large amounts in these cells. Ongoing research is exploring the significance of this granzyme B production in these cells, and whether it might be contributing to the death of the chronic lymphocytic leukemia cells.

Signal Transduction Inhibitor Therapy for Lymphoma

In order to advance the treatment of lymphoma new treatment approaches are needed to target different pathways in lymphoma cells. Malignant lymphoma cells respond to signals that are delivered to the outside of the cell that cause a reaction inside the cell. These signaling pathways have now become the focus of many new drugs. These drugs are referred to as "signal transduction inhibitors." These agents have a mechanism of action that is quite different than traditional chemotherapy or immunotherapy. In this project we are using an inhibitor of the mammalian target of rapamycin (mTOR) called everolimus. We have previously demonstrated in trials using only everolimus that approximately 30% of patients with Diffuse Large B-cell Lymphoma will have an antitumor response. In patients with relapsed Hodgkin's disease response rate was as high as 45%. The SPORE is currently conducting LS 0689 -- a clinical trial that combines everolimus with sorafenib for relapsed lymphoma. This trial is enrolling patients at the University of Iowa and at the Mayo Clinic the trial has completed the Phase I portion and found that sorafenib 200 mg twice daily combined with everolimus 5 mg daily was a safe combination. The trial has now moved to a Phase II portion. A total of 62 patients have now been en rolled on this study. Our hypothesis is that targeting two pathways with two different pills will produce a better response rate.

Biology and Epidemiology of APRIL and BLyS in B-cell NHL

Non-Hodgkin lymphoma (NHL) is caused by unregulated growth of human B lymphocytes, commonly referred to as white blood cells. Under normal conditions, lymphocytes must strictly regulate their growth to provide adequate defenses against infection. At the same time, these same lymphocytes must be kept in check so they do not overwhelm the immune system with inappropriate cell numbers. Maintaining a normal balance between cell growth and death is critical to our immune system, and often, dysregulation in this balance is found in lymphoma. Soluble factors, often called cytokines, are present in our blood and tissue and they play an important role is regulating lymphocytes, some cause cells to grow and others inhibit their growth. One of these factors is called BLyS, or B lymphocyte stimulator. Recent studies by our group, as well as others, have shown that BLyS is important in both normal B lymphocyte biology and in B cell cancers like lymphoma. We have found that BLyS levels are elevated in patients with NHL and that BLyS and its receptors prevents tumor cells from dying. The underlying cause of elevated BLyS levels has not been identified and through research funded by the SPORE program we aim to determine if genetic variation in BLyS and BLyS-related genes is associated with the development of lymphoma and NHL patient survival. Initial results from our SPORE project, published in Cancer Research, indicate that inherited variation in the BLyS gene is associated with elevated BLyS levels and development of lymphoma. In addition to our studies on BLyS we also propose to study the impact of APRIL, a BLyS related protein, on the growth and survival of malignant B cells. Work from this aim of the grant, published in Blood, has revealed that APRIL promotes NHL tumor cell growth. Taken together our SPORE project studies suggest that identification of patients who have lymphoma-associated genetic variation in BLyS or BLyS-related genes, or a predisposition to elevated BLyS or APRIL levels, could provide us with an opportunity to better understand the significance of these molecules in B cell malignancies and ultimately to translate these findings to improved clinical management and perhaps novel therapeutic approaches.

Targeted Therapy Exploiting the Malignant B-cell Microenvironment Interface

Just as we, in our entirety as humans, depend on the support of other individuals and infrastructure in our daily lives, lymphoma and other cancer cells depend on the support of many other cell types in the body for survival and growth. The best example of this, is that lymphoma cells taken from the patient do not grow in tissue culture. Clearly, the support of a host is needed for lymphoma to survive. In fact, cancer cells have many ways of communicating their needs to surrounding host cells or their microenvironment to obtain necessary support. The support of other cells and body structures is critical for lymphoma cells to survive exposure to chemotherapy. Consequently, the failure of cancer treatment is often related to the assistance that other cells in the body give to the tumor. Eliminating this support is critical for successful lymphoma therapy.

We have now shown that we can disrupt the interaction between the tumor and the microenvironment – primarily by blocking a molecule known as VLA-4. This can be achieved with anti VLA-4 antibodies. We have shown that depriving lymphoma cells from the support of surrounding cells makes these cells sensitive to chemotherapy. We took our observations forward and showed that similar mechanisms apply when treating with monoclonal antibodies like rituximab. We can now make lymphoma cells more sensitive to rituximab therapy by interfering with their cross talk with surrounding cells.

In order to cure lymphoma, we will have to focus not only on cancer cells but the support cancer cells receive from surrounding host tissues and organs. We just made an important step forward in moving therapy targeting both – lymphoma cells and supporting cells within the host to the clinic.

Monoclonal Antibody Induced NK Cell Activation & Complement

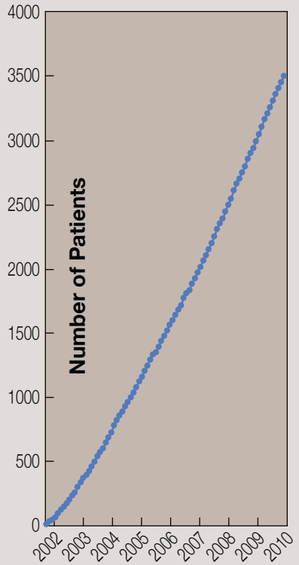
Monoclonal antibodies are now a standard part of treatment for both lymphoma and chronic lymphocytic leukemia, however, we still do not fully understand how they work. Preliminary results in the research laboratory suggest they may work differently depending upon how much monoclonal antibody is given. In this project, we will evaluate blood samples from lymphoma patients soon after they are treated with the monoclonal antibody known as rituximab to assess the effect the treatment is having on the immune system. In addition, we will study the effects of a novel treatment combination in chronic lymphocytic leukemia patients using a combination of pentostatin, alemtuzumab, and lower doses of rituximab (PAR regimen) at the University of Iowa and Mayo Clinic. This project is designed to teach us more about how monoclonal antibodies work, and most importantly to use this information to develop new approaches to using them with the goal of improving the response to therapy.

TH17 and Regulatory T-Cell Interactions in B-Cell Non-Hodgkin Lymphoma

TH17 cells and regulatory T-cells (Treg cells) are normal immune cells that are usually present inside lymph nodes involved by non-Hodgkin lymphoma cancer cells. TH17 cells are able to cause an inflammatory response that may help the immune system respond to the cancer cells. In contrast, Treg cells suppress the immune system and "switch off" any response to cancer cells. TH17 and Treg cells originate from the same parent cell and usually there is a balance between the cells that promote the immune response and those that suppresses it. Our research has shown that in lymph nodes involved by lymphoma, the balance between these two types of cells is significantly skewed in favor of Treg cells and that the lymphoma cancer cells play a role in tipping the balance toward an immunosuppressive environment. Our work is currently focusing on how the lymphoma cancer cell does this and on ways to restore the balance.

Update on the Lymphoma and Leukemia SPORE Registry *and* Frequently Asked Questions

Total number of patients enrolled into the SPORE Registry by year of enrollment



Where are we now?
We continue to have high participation of newly diagnosed lymphoma and chronic lymphocytic leukemia patients into the SPORE registry. As of October 2009, we have enrolled 3,442 patients at Mayo Clinic and University of Iowa. This large number of patients means we can answer more questions faster and with greater statistical precision than is possible with smaller studies. We can also begin to address questions for specific subtypes of lymphoma and leukemia.

Follow-up is important! Your experience after diagnosis and treatment is critical to helping us understand how to best manage lymphoma and leukemia, and to do this it is important to hear from everyone possible, including those who are doing well. This is why we contact participants every six months for the first three years after their diagnosis, and then annually after that. We are very encouraged by your commitment, to date, only 7 participants out of over 3,400 have withdrawn from follow-up! But please remember, it is your choice to whether you want to stay in the follow-up program, and your choice does not impact your clinical care.

Recent Findings
One of the recent studies from the SPORE Registry asked the question of whether it was safe for patients to use their statin medications after lymphoma diagnosis. A laboratory study suggested that statins might interfere with how drug rituximab works. Rituximab is used to treat many types of lymphoma, and has greatly improved survival rates. Using data from the SPORE Registry, we found that in diffuse large B-cell lymphoma (DLBCL) treated with rituximab plus chemotherapy ("R-CHOP"), there was no difference in outcome for patients who did or did not use statins. This was also true for follicular lymphoma patients. These results were presented at the 2008 American Society for Hematology meeting and were just published in the Journal of Clinical Oncology, the top journal for oncologists. These results do not support removing patients from statins during or after therapy.

Study Team Updates-Mayo Clinic Rochester
The Rochester team consists of five study coordinators, all of whom might contact you by phone, mail or within the clinic to complete follow-ups. The study team consists of; Sara Bonde, Amy Eisenberg, Jennifer Vogel, Julianne Lunde and Olga Richter.

Study Team Updates-University of Iowa
The University of Iowa team consists of three study coordinators who follow patients in our various cancer registries and may contact you by mail or during one of your visits to the Holden Comprehensive Cancer Center in Iowa City. Our team members are Laura Jacobus, Tina Knutson and Allison Knutson (no relation – everyone asks!)

Frequently Asked Questions
Many participants have several questions both at consent and during the follow up interviews. Below you will find some of the most frequently asked questions and answers.

This study is an Epidemiological Study, what does that mean, and what is the difference between this and a Clinical Trial?
The SPORE Registry is an epidemiological study. This means that we do not assign any therapy or interventions for your disease, but rather track (through surveys and medical records) the care you normally receive (as if you were not in a study) and the outcomes you experience. This is in contrast to a clinical trial, where a participant is given some type of intervention – for example, randomized to one treatment or another. Both types of studies are important for medical progress. An epidemiological study is able to study many more types of questions than a clinical trial, but a clinical trial provides a stronger answer, particularly related to new treatments.

Why are there so many questions asking about different diseases? Will I get these diseases because of Lymphoma/CLL or treatment?
While we do not expect most people to develop these health problems, a small number of patients may develop them. The way we find out why some people develop problems is by studying everyone, and comparing who does and does not do well. Thus, we need to ask these questions of everyone. This information helps us identify the small groups of patients who may develop health problems to find ways to prevent these complications.

Can I still participate in the study if I lived in the Midwest when I consented to the study and now live out of the area?
Yes! Once you are enrolled in the SPORE Registry, we will continue to follow you where ever you move. It helps us if you can provide address updates so we know how to best contact you.

Thank you for your participation
We want to take this opportunity to once again express our sincere appreciation for participating in this study. It is only through people like you who are willing to take the time necessary to participate and share information that are we able to conduct this research. We realize that at the time we approach you in the clinic/hospital to participate in the study, you may have just learned about your diagnosis and that you may have many new questions about the study once you return home. Please feel free to contact us at any time at the contact numbers below. We are happy to answer any question you may have.

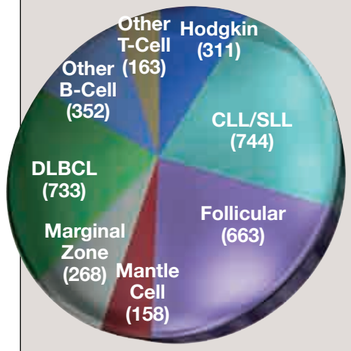
University of Iowa Study Coordinators:

From left to right: Tina Knutson, Allison Knutson, Laura Jacobus

Mayo Clinic Study Coordinators:

From left to right: Jenny Vogel, Olga Richter, Julianne Lunde, Amy Eisenberg, Sara Bonde

NHL Subtypes SPORE, November 2009



MER Accrual by Month