The following abstracts related to the SPORE were selected for presentation at this year's American Society of Hematology meeting, held December 5-8, 2015.

A Clinicogenetic Risk Model (m7-FLIPI) Prospectively Identifies One-Half of Patients with Early Disease Progression of Follicular Lymphoma after First-Line Immunochemotherapy
Jurinovic Vindi, Robert Kridel, Annette M Staiger, Monika Szczepanowski, Heike Horn, Martin Dreyling, Andreas Rosenwald, German Ott, Wolfram Klapper, Andrew Zelenetz, Jonathan Friedberg, Stephen Ansell, Laurie Sehn, Joseph Connors, Randy Gascoyne, David Weinstock, Wolfgang Hiddemann, Michael Unterhalt, Eva Hoster, Oliver Weigert

Activity of Idelalisib in High-Risk Follicular Lymphoma with Early Relapse Following Front Line Immunochemotherapy
Ajay Gopal, Brad Kahl, Christopher Flowers, Peter Martin, Brian Link, Stephen Ansell, Wei Ye, Brian Koh, Steve Abella, Paul Barr, Gilles Salles, Jonathan Friedberg

Brentuximab Vedotin with RCHOP As Frontline Therapy in Patients with High-Intermediate/High-Risk Diffuse Large B Cell Lymphoma (DLBCL): Results from an Ongoing Phase 2 Study
Christopher Yasenchak, Ahmad Halwani, Ranjana Advani, Stephen Ansell, Lihua Elizabeth Budde, John Burke, Charles Farber, Beata Holkova, Luis Fayad, Kathryn Kolibaba, Mark Knapp, Martha Li, Thomas Manley, Dipti Patel-Donnelly, Mahesh Seetharam, Habte Yimer, Nancy Bartlett

Comprehensive Analyses of Genetic Features Identify Coordinate Signatures in Diffuse Large B-Cell Lymphoma
Bjoern Chapuy, Andrew Dunford, Chip Stewart, Atanas Kamburov, Jaegil Kim, Margaretha Roemer, Marita Ziepert, Amy Jiayue, Mike Lawrence, Julian Hess, Mara Rosenburg, Amaro Taylor-Weiner, Robert Redd, Heike Horn, Anne Novak, James Cerhan, Thomas Haberman, Andrew Feldman, Brian Link, Todd Golub, Donna Neuberg, German Ott, Reiner Siebert, Andreas Rosenwald, Gerald Wulf, Stefano Monti, Scott Rodig, Markus Löffler, Michael Pfreundschuh, Lorenz Trümper, Gad Getz, Margaret Shipp

Event-Free Survival at 12 Months and Subsequent Overall Survival in Patients with Peripheral T-Cell Lymphoma
Matthew Maurer, Fredrik Ellin, James Cerhan, Stephen Ansell, Brian Link, Mats Jerkeman, Karin Smedby, Carrie Thompson, William Macon, Sergei Syrbu, Susan Slager, Thomas Witzig, Thomas Habermann, Thomas Relander, Andrew Feldman

Everolimus Plus RCHOP-21 Is Safe and Highly Effective for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Results of the Phase I Trial NCCTG1085 (Alliance)
Patrick Johnston, Betsy Laplant, Ellen McPhail, Thomas Habermann, David Inwards, Ivana Micallef, Joseph Colgan, Grzegorz Nowakowski, Stephen Ansell, Thomas Witzig

Five-Year Survival Data Demonstrating Durable Responses from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma
Robert Chen, Ajay Gopal, Scott Smith, Stephen Ansell, Joseph Rosenblatt, Kerry Savage, Joseph Connors, Andreas Engert, Emily Larsen, Dirk Huebner, Abraham Fong, Anas Younes

Identification of USP14 and UCHL5 As Druggable Oncotargets in Ibrutinib-Resistant Mantle Cell Lymphoma
Aneel Paulus, Sharoon Akhtar, Kelara Samuel, Hassan Yousaf, Davitte Cogen, Pooja Advani, Thomas Witzig, George Weiner, Sikander Ailawadhi, Joachim Gullbo, Stig Linder, Geraldo Otero-Colon, Kasyapa Chitta, Asher Alban Chanan-Khan

Incidence and Outcomes of Treatment Refractory Diffuse Large B-Cell Lymphoma in the Immunochemotherapy Era
Matthew Maurer, Carrie Thompson, Umar Farooq, Tasha Lin, Grzegorz Nowakowski, Yi Lin, Ivana Micallef, Anne Novak, William Macon, Sergei Syrbu, James Cerhan, Thomas Witzig, Thomas Habermann, Stephen Ansell, Brian Link

Lymphocyte-to-Monocyte Ratio at Diagnosis and Survival in De Novo Double/Triple Hit Diffuse Large B-Cell Lymphoma
Luis Porrata, Kay Ristow, Ellen McPhail, William Macon, Matthew Maurer, Grzegorz Nowakowski, Stephen Ansell, Thomas Witzig, Svetomir Markovic, Thomas Habermann

Multiparametric Analysis of Intra-Tumoral T-Cells in Hodgkin's Lymphoma Using Mass Cytometry (CyTOF)
Jose Villasboas Bisneto, Stephen Ansell

Mutations Targeting the ErbB Pathway and MSC in Peripheral T-Cell Lymphoma
Michael Zimmermann, Surendra Dasari, Rebecca Boddicker, Yu Zeng, Bruce Eckloff, Julie Cunningham, Yanhong Wu, Julie Porcher, Brian Link, Stephen Ansell, James Cerhan, Jean-Pierre Kocher, Andrew Feldman

Natural History of Central Nervous System Relapse in Diffuse Large B Cell Lymphoma in the Immunochemotherapy Era
Gita Thanarajasingam, Matthew Maurer, Umar Farooq, Patrick Johnston, Carrie Thompson, Stephen Ansell, Luis Porrata, William Macon, Sergei Syrbu, James Cerhan, Thomas Habermann, Thomas Witzig, Brian Link, Grzegorz Nowakowski

Nivolumab in Patients (Pts) with Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL): Clinical Outcomes from Extended Follow-up of a Phase 1 Study (CA209-039)
Stephen Ansell, Philippe Armand, John Timmerman, Margaret Shipp, M. Brigid Bradley Garelik, Lili Zhu, Alexander Lesokhin

PD-1 Blockade with Pembrolizumab (MK-3475) in Relapsed/Refractory CLL Including Richter Transformation: An Early Efficacy Report from a Phase 2 Trial (MC1485)
Wei Ding, Haidong Dong, Timothy Call, Tait Shanafelt, Sameer Parikh, Jose Leis, Betsy Laplant, Rong He, Thomas Witzig, Yi Lin, Asher Chanan-Khan, Deborah Bowen, Michael Conte, Thomas Habermann, David Viswanatha, Ivana Micallef, Neil Kay, Stephen Ansell

Preliminary Safety and Efficacy of the Combination of Brentuximab Vedotin and Ipilimumab in Relapsed / Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412)
Catherine Diefenbach, Fangxin Hong, Jonathon Cohen, Michael Robertson, Richard Ambinder, Timothy Fenske, Ranjana Advani, Brad Kahl, Stephen Ansell

Preliminary Results from a Phase 1/2, Open-Label, Dose-Escalation Clinical Trial of IMO-8400 in Patients with Relapsed or Refractory Waldenstrom's Macroglobulinemia
Sheeba Thomas, Wael Harb, Joseph Thaddeus Beck, Gabrail Nashat, M. Lia Palomba, Stephen Ansell, Herbert Eradat, Edward Libby III, Ranjana Advani, Julio Hajdenberg, Leonard Heffner, James Hoffman, David Vesole, Lindsey Simov, Nancy Wyant, Julie Brevard, James O'Leary, Sudhir Agrawal

Prognostic Correlates and Outcomes of Relapsed T-Cell Acute Lymphoblastic Leukemia/Lymphoma: An Analysis of 41 Consecutive Patients
Tasha Lin, Hassan Alkhateeb, Aref Al-Kali, Michelle Ann Elliott, Naseema Gangat, William Hogan, Grzegorz Nowakowski, Carrie Thompson, Thomas Witzig, Stephen Ansell, Mark Litzow, Mrinal Patnaik

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The Exhausted Intratumoral T Cell Population in B-Cell Non-Hodgkin Lymphoma Is Defined By LAG-3, PD-1 and tim-3 Expression
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Tissue Is the Issue: Accuracy of PET Imaging to Detect Bone Marrow Clearance in Patients with Peripheral T-Cell Lymphoma
Anthony Pham, Stephen Broski, Thomas Habermann, Dragan Jevremovic, Gregory Wiseman, Andrew Feldman, Matthew Maurer, Kay Ristow, Thomas Witzig

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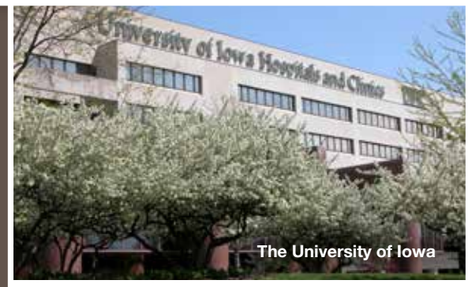
University of Iowa Health Care
NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute
Mayo Clinic Cancer Center

SPORE

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



The University of Iowa


Mayo Clinic

The University of Iowa/Mayo Clinic (UI/MC) Lymphoma SPORE is a dynamic, productive, translational cancer research program based at two comprehensive cancer centers.

The UI/MC SPORE was first funded in 2002 and competitively renewed by the National Cancer Institute in 2007 and 2012. The key to the ongoing success of the UI/MC SPORE is the collaborative interaction between investigators at Iowa and Mayo. This includes researchers with expertise in basic laboratory, clinical and population-based lymphoma research. The overall goal of the SPORE is to support innovative, interactive, translational research into lymphoma and chronic lymphocytic leukemia that leverages the expertise of laboratory, clinical, and population-based research at both institutions.

Drs. Weiner and Witzig serve as co-Principal Investigators (PIs) on the SPORE. Serving as co-PIs allows us to represent investigators of the two institutions equally and effectively. The SPORE provides direct support for lymphoma research while also providing resources for lymphoma research supported by other mechanisms.

The SPORE team is deeply indebted to the many patients who have agreed to participate in research studies and have made the progress of the SPORE possible, as well as to the many volunteers and researchers who have contributed the success of these programs.

We are proud to have contributed to the many advances in lymphoma therapy that have taken place since the SPORE was initiated, and look forward to informing you about our research results as we continue to make progress against lymphoma and related diseases.

As we have done in the past, we have included a summary of the four major research projects as well as the four Shared Lymphoma Research Cores that are supported through the UI/MC SPORE and are vital to the success of the SPORE research projects.

- Clinical Research Core accrues subjects to therapeutic and observational studies such as the Molecular Epidemiology Resource.
- Biospecimens Core supports the processing and evaluation of samples after they are collected by the Clinical Research Core. It provides these samples to investigators working on multiple research projects.
- Biostatistics and Bioinformatics Core works with each of the research projects by providing biostatistics and bioinformatics support. In addition, it works closely with both the clinical research core and biospecimens core on data storage and analysis.
- Administrative Core works with each of these cores to support and link lymphoma research activities at the two institutions.

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

Patient Story: Rick Noeth

Rick Noeth

Since I was four years old I have always loved to swim. I have been a U.S. and Iowa Masters swimmer for decades (breaking nearly 30 records over the years), and 2012 was an especially fun year in the pool for me. So when I started having some back pain in December of that year, I just assumed it was a muscle strain. Then on a trip to LA in January, when my back pain became suddenly intense, with corresponding leg pain – requiring a wheelchair to get back through the airports, I knew something was seriously wrong. I had an MRI the day after I got home and was told I had a spine tumor that was crushing one of the nerves that helped control my ability to stand and walk.

My initial treatment included a six-hour spine surgery which removed most of the tumor, but the report came back that it was an aggressive Lymphoma. My treatment then included six rounds of outpatient RCHOP, two 5-day hospital stays for high-dose methotrexate, and 20 sessions of radiation. I was in the wheelchair for many months and my white blood counts were so low that the only place I went for seven months was to the hospital. I found that during my illness, the best way to cope with everything was to persistently focus on taking things day by day, sometimes hour by hour. And I always rewarded myself every night (without fail) with a bowl of ice cream (I'm partial to chocolate chip!).

So, given that in the spring of 2015 I was 18 months in remission (although still suffering from some ongoing side/late effects), I wanted to do something special to celebrate National Cancer Survivors Day. And since I was now able to get back in the pool 2-3 times a week, I entered three swimming events at the Quad Cities Senior Games held on June 6 at Augustana College in Illinois (about an hour from our Iowa City home – which was the furthest I had travelled since early 2013).

As I was warming up before my first swimming event, so much of the past 2½ years was running through my mind. It was nearly overwhelming to think of how sick I had been and all of the doctors, nurses, and technicians who played such a role in my treatment and recovery. So I focused solely on the opportunity I was given to again do what I love and was thinking that this first meet back was a way to honor my incredibly skilled and compassionate team at the Holden Comprehensive Cancer Center here at the University of Iowa who not only saved my life, but now helped me to swim again. Long story short: 3 gold medals and 3 Quad Cities Senior Games records (100, 200, 500 yard freestyle events)! I could not be more grateful.

The 2015 Spore Retreat

NHL/CLL Family Study Summary

We continue to recruit families for our Family study of B-cell malignancies. To date, we have 1,960 participants from 472 families. We appreciate the time and effort our participants contributed to our study.

For those not familiar with factors associated with risk of chronic lymphocytic leukemia (a subtype of non-Hodgkin lymphoma), age, male sex, and Caucasian race are consistently associated with risk. However, having a family history of chronic lymphocytic leukemia (CLL) or other blood cancers is the strongest risk factor known to date. Thus, our research focus has been to identify inherited genetic variants that are associated with CLL risk.

As we shared in our last update, we participated in an international lymphoma project known as the "NHL GWAS". A genome-wide association study, or GWAS, is when genetic variants are studied in individuals to determine if any of the variants are associated with a specific disease. The NHL GWAS project included 22 different study groups from North America, Europe, and Australia, each of whom contributed thousands of cases of non-Hodgkin lymphoma (NHL) subtypes, including CLL. A new NHL GWAS consortium paper on CLL is currently under peer-review at a journal. In that paper, we reported additional new genetic variants that are common in the general population but have modest effect on risk of CLL. These new variants along with the ~30 other variants that we and others have identified will help us understand the underlying pathobiology of CLL.

We have also started to evaluate the role that lower-frequency genetic variants have on risk of CLL. We used a technique known as next generation sequencing. We selected 93 families that had at least two members with CLL from the Family Study of B-Cell Malignancies. We sequenced all the genes from 443 family members; 160 with CLL, 73 individuals with the precursor condition, monoclonal B cell lymphocytosis, and 210 relatives without CLL. We then performed statistical analyses to find chromosomal regions that were inherited in the majority of CLL families. We have 6 regions of strong interest to us. We are in the process of validating these findings in new families from our study as well as with our collaborators at the National Cancer Institute.

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

Mayo Clinic
Catie Erding
855-899-0693
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Meet Our Investigators

GAIL BISHOP, PHD

Principal Investigator, Developmental Research Project

Gail Bishop is a Professor of Microbiology and Internal Medicine at the University of Iowa, where she serves as Associate Director for Basic Science Research of the Holden Comprehensive Cancer Center. Gail grew up in Milwaukee, WI, earned her B.A. in Biology at St. Olaf College in Northfield, MN, an M.S. in Oncology at The University of Wisconsin-Madison, and her Ph.D. in Cellular & Molecular Biology at The University of Michigan. She performed postdoctoral research at The University of North Carolina before joining the faculty at U Iowa in 1989. Gail has a career-long interest in molecular mechanisms of lymphocyte function and cancers of B cells. The theme of her B cell studies is to understand how signals delivered to the B cell from its environment control B cell survival and activation. In the past several years, studies of lymphoma patients have shown that a substantial number of their tumors are deficient in a cell signaling protein called TRAF3 that Gail and her lab study. This protein normally keeps B cells from surviving inappropriately. Gail and her group are working to understand how TRAF3 regulates B cell survival, so the most effective possible therapies can be used to block abnormal survival of malignant B cells that don't have sufficient amounts of TRAF3. Gail benefits greatly from combining her basic research knowledge with the clinical expertise of her SPORE investigator colleagues, and her SPORE developmental project is aimed at translating her basic findings to human patient tumors. She is also very passionate about training the next generation of biomedical researchers. In addition to her classroom teaching, she has mentored > 20 graduate students to successful completion of the PhD degree, including MD-PhD students. Gail has been married for 38 years to Warren Bishop, a pediatric gastroenterologist, and together they raised two sons, Eric and Ian. Outside of work, she enjoys hiking, cooking, and reading mystery novels, as well as jewelry making and wirework.

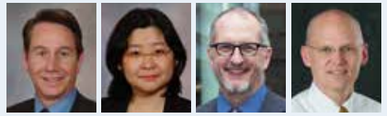
ANDREW FELDMAN, MD

Director, Biospecimens Core

Andy Feldman is a hematopathologist and Associate Professor of Laboratory Medicine and Pathology at Mayo Clinic. He grew up in the Boston area and did his undergraduate and medical studies at Brown University in Rhode Island. He completed research training, pathology residency, and a hematopathology fellowship at the National Cancer Institute before joining Mayo in 2006. His research has focused on molecular profiling of T-cell lymphoma, with the aim of discovering and developing clinical biomarkers that refine the pathologic classification of lymphomas and help stratify patients for individualized therapy. Andy has enjoyed working with the University of Iowa/-Mayo Clinic SPORE research team since starting at Mayo. He is grateful to have received funding early in his career through the SPORE Career Development Program and the Damon Runyon Cancer Research Foundation, both of which allowed him the opportunity to gain critical skills and develop long-lasting collaborative relationships with members of the SPORE. Andy became Director of the SPORE Biospecimens Core in 2013. Outside of work he enjoys music, hiking, baseball, and spending time with his wife Daly and daughter Alma.

PROJECT 1
The Role of Monocytes in non-Hodgkin Lymphoma

Project Leaders: Stephen Ansell, MD, PhD (Mayo) and Wei Ding, MD (Mayo) Co-Investigators: Allan Dietz, PhD (Mayo) and Brian Link, MD (Iowa) Dr. Stephen Ansell, Dr. Wei Ding, Dr. Allan Dietz



Dr. Stephen Ansell Dr. Wei Ding Dr. Allan Dietz Dr. Brian Link

Tumor tissue in patients with non-Hodgkin lymphoma contains not only cancer cells but normal immune cells as well. However, the normal immune cells present in the lymph node are not successful in killing the malignant cells but rather appear to play an important role in supporting the growth of the malignant lymphoma cells. Cells in the tumor called monocytes appear to be particularly important. We have found that monocytes in the tumor suppress other immune cells and prevent the immune system from adequately reacting to the presence of cancer cells. Suppressive monocytes are frequently found in the peripheral blood and tumors of lymphoma patients and these cells promote the growth of lymphoma cells. Monocytes also protect lymphoma cells from chemotherapy.

We are currently testing ways to interfere with the signals from monocytes that are used to support cancer cell growth and to suppress the patient's anti-tumor immunity. Practically, we are testing whether we can block the suppressive signals that shut down normal T-cell function. We are using a blocking antibody to prevent signaling through PD-1, a receptor on T-cells. PD-1 is the "off switch" on T-cells that suppresses their function. By blocking this receptor, the "off" message is not received by the T-cells and the normal immune response remains active. We are testing whether this results in clinical benefit for lymphoma patients. This study is open and accruing patients and we are doing correlative studies to measure immune function after treatment.

PROJECT 2
In Situ Immunization using Nanoparticles

Project Leaders: George Weiner, MD (Iowa), Brian Link, MD (Iowa), and Aliasger Salem, PhD (Iowa)

Dr. George Weiner Dr. Brian Link Dr. Aliasger Salem

Our project is focused on a three-step approach to enhancing the ability of the immune system to reject lymphoma. The first step involves inducing the local death of lymphoma cells in a way that allows the immune system to react to molecules in the lymphoma. This is called immunogenic tumor cell death and is induced by loading nanoparticles with the chemotherapeutic drug Doxorubicin and injecting them directly into a lymphoma. The next step is enhancing the ability of the immune system to respond strongly to the molecules in the lymphoma that have been released. This has been achieved by co-delivering a medicine that stimulates the immune system along with the doxorubicin from the nanoparticle. The third and final step is sustaining the immune response to the lymphoma. This three step approach has proven to be effective in mouse models of lymphoma and can result in regression of not only the treated lymphoma mass but lymphoma elsewhere in the body. Plans are ongoing to test it in patients with lymphoma.
This research has been published in the following journals:

1. Three steps to breaking immune tolerance to lymphoma: a microparticle approach. Makkouk A, Joshi VB, Lemke CD, Wongrakpanich A, Olivier AK, Blackwell SE, Salem AK, Weiner GJ. *Cancer Immunol Res.* 2015 Apr;3(4): 389-98. doi: 10.1158/2326-6066.CIR-14-0173. Epub 2015 Jan 27.
2. Biodegradable microparticles loaded with doxorubicin and CpG ODN for in situ immunization against cancer. Makkouk A, Joshi VB, Wongrakpanich A, Lemke CD, Gross BP, Salem AK, Weiner GJ. *AAPS J.* 2015 Jan;17(1): 184-93. doi: 10.1208/s12248-014-9676-6. Epub 2014 Oct 18.

PROJECT 3
Targeting JAK2 Kinase in Lymphoma

Project Leaders: Mamta Gupta, PhD (Mayo) and Thomas Witzig, MD (Mayo)

This project is investigating a signaling pathway that cancer cells used to grow and divide. It is referred to as the JAK/STAT pathway. Our group has shown that the STAT3 pathway is activated in certain types of diffuse large B cell lymphoma, the most common lymphoma in the United States. We have also shown that the secretion of immunoglobulin light chains from these lymphoma cells is an important prognostic factor for lymphoma and can be inhibited by specific drugs that target the JAK/STAT pathway. We have taken this observation into the clinic and are performing a clinical trial using an oral JAK1/JAK2 inhibitor called ruxolitinib. Ruxolitinib is already approved by the FDA for other types of cancer. We are trying to establish whether or not the drug can be effective in lymphoma. This trial is ongoing. We have also performed preclinical work in the laboratory using a second STAT3 inhibitor called OPB-111077. This is another oral agent that works potentially through this pathway as well as inhibiting tumor metabolism. This trial has opened and two patients have been accrued.

In further work with lymphoma samples and cell lines, we have performed epigenetic mechanisms of constitutive STAT3 signaling. We focused on the tyrosine phosphatases such as PTPN6, which has been shown to be negatively regulated STAT3 signaling. In our data set, PTPN6 was found silenced and hypermethylated at CPG2 islands in majority of the diffuse large B cell lymphoma (DLBCL) patients. We were able to reactivate this negative control mechanism with a commonly used drug, 5-azacytidine, a DNA methyltransferase inhibitor and with the histone deacetylase inhibitor LBH589. This study was presented at ASH 2013 annual meeting and later published in Leukemia journal. LBH589 is being used for lymphoma in another clinical trial supported in part by the Lymphoma SPORE Project 3. We have treated over 100 patients and the results should be forthcoming soon.

We have performed the genetic studies to better understand why STAT3 is activated in DLBCL. We documented that mutations in JAK2 are rare; however, we found a novel missense (M206K) STAT3 mutation in diffuse large B cell lymphoma that alters STAT3 signaling. These important studies shed important light on the importance of this pathway. This study is published in *PLOS ONE* journal.

We also performed a comprehensive study in T cell lymphoma and found that majority of subtypes of PTCLs (ALCL, PTCL NOS, NK T cell, Angioimmunoblastic TCL) have constitutive STAT3 activation and correlated with bad prognosis. Inhibitors of JAK pathway such as Ruxolitinib and TG101348 inhibited the STAT3 signaling in TCL. This study was presented at ASH 2013 meeting. Another approach to altering signaling and perhaps inhibiting tumor growth is to interfere with the signals that activate the pathway. These signals are referred to as cytokines. Several cytokines including IL-10, sIL-2Ra, Rantes and IL-15 were secreted by TCL cell lines of various origins. We are completing an important study that tested serum from patients with mantle cell lymphoma and T-cell lymphoma to learn which cytokines were elevated and whether or not the elevation was predictive of survival. This will help us to design ways to interfere with these important cytokines.

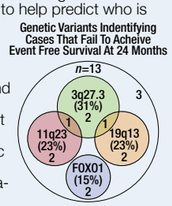
In summary, the project is been very productive and these basic findings are now being translated into clinical trials.

PROJECT 4
Genetic Epidemiology and Function of Germline and Somatic Variants in DLBCL

Project Leader: James Cerhan, MD, PhD (Mayo) and Anne Novak, PhD (Mayo)
Co-Investigator: Yan Asmann, PhD (Mayo) and Susan Slager, PhD (Mayo)

Left to right:
Dr. Anne Novak, Tammy Price-Troska, Dr. Jim Cerhan, Tammy Rattle

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) subtype. Project 4 is focused on understanding how genetics influences DLBCL development and progression, and is looking at two types of genetics. The first is "host" genetics—this is the genetic make-up of each person that is inherited from their parents, and we use DNA collected from a blood sample to characterize this type of genetic variation. The second is "tumor" genetics these are the genetic changes that occur in cells that can lead to cancers. Here, we study DNA extracted from tumor tissue collected as part of the diagnosis. We hope that by studying both of these types of genetics we can better understand what causes DLBCL to develop, and once it has developed, ways we might "treat" these genetic changes to eliminate or control the cancer. To achieve these goals, we are assisted by our extensive and well characterized SPORE participants who are enrolled in the Molecular Epidemiology Resource, as well as an international consortium of lymphoma investigators called InterLymph. In total, we are using data from over 3000 DLBCL patients and 10,000 controls to find new genetic causes of DLBCL. We recently led a paper published in Nature Genetics that identified four loci associated with risk of DLBCL. These data provide substantial new evidence for genetic susceptibility to this B-cell malignancy and point to pathways involved in immune recognition and immune function in the pathogenesis of DLBCL. Future goals are to understand the underlying mechanism of these variants and to use these and additional genetic results to develop a "risk" score to help predict who is at high risk of DLBCL. We are also using our next generation sequencing data of all the coding regions of the genome of DLBCL samples to identify and characterize genetic changes in tumors. In our recent manuscript entitled "Whole-Exome Analysis Reveals Novel Somatic Genomic Alterations Associated with Outcome in Immunochemotherapy-Treated Diffuse Large B-Cell Lymphoma" published in *Blood Cancer Journal* we used genetic information from 51 newly diagnosed and immunochemotherapy treated DLBCL patients to evaluate the association of genomic alterations with patient outcome. We identified a panel of genes with mutations and chromosomal copy number alterations that were associated with poor outcome. Integration of the genetic data revealed that 77% of patients who fail to achieve event free survival within 24 months of diagnosis have a combination of four variants (*FOXO1* mutation and gains in 3q27.3, 11q23.3, and 19q13.32 (Figure). These genetic biomarkers of clinical failure may provide us with additional tools to better stratify newly diagnosed cases of DLBCL. Further validation of these studies is ongoing in additional cases of DLBCL and our next step will be to integrate the tumor data with our host genetic data. Once complete, we will take the most relevant genetic changes that we find back to the laboratory to understand how they impact biology and how we might develop therapies to block these impacts. If successful, our project should provide insights into lymphoma biology that can be used clinically for disease risk assessment, putting patients into groups for treatment, and identification of new treatment targets.



Administrative Core

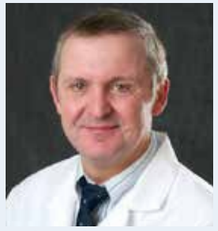
The Administrative Core is the organizational hub of the SPORE. Drs. George Weiner and Thomas Witzig are Co-Principal Investigators of the SPORE and cooperate to provide leadership and direction. The Administrative Core provides the organizational structure to coordinate the activities of the research projects, scientific cores and developmental programs at both institutions. The infrastructure to support collaboration, financial management, and procedures for review of research projects and project growth and coordinating communication between Iowa and Mayo, patient advocates and NCI is provided through this Core. The Administrative Core also coordinates the publicity and the selection process for the Developmental Research and Career Development Awards.

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

Thomas E. Witzig, MD
Mayo Clinic Cancer Center

Biospecimen Core

The Biospecimen Core is responsible for the collection, processing and storage of all blood samples that are collected from participants. In addition, tumor samples are processed and stored. Another function of the Biospecimen Core is to build tissue micro arrays (TMAs). A TMA is a paraffin (wax) block where cores of tumor blocks are placed together on one block, so multiple samples can be studied at one time. The Biospecimen Core also devotes time to developing new lab methods. The members of the Biospecimen Core and the number of samples currently managed by the Biospecimen Core can be found in the tables below:



Dr. Sergei Syrbu - *Iowa*

Dr. Andrew Feldman - *Mayo*

Dr. Ann Novak - *Mayo*

Name	Title	Role
Andrew Feldman, MD	Hematopathologist	Core director
Sergei Syrbu, MD	Hematopathologist	Core co-director
Anne Novak, PhD	Assistant Professor of Medicine	Co-Investigator
Tammy Rattle	Lab Technician	Processes all lymphoma samples
Lindsay	Clinical Research Coordinator	Manages samples used in projects
Julianne Lunde	Program Manager	Oversees project movement through core

Biospecimens Samples managed by the Core:

Subtype	Peripheral Blood DNA	DNA from tumor	Serum	Plasma	Cells from tumors
Composite Histology	281	39	207	194	32
Diffuse large B-Cell lymphoma (DLBCL)	1299	209	1008	934	46
Follicular lymphoma	1079	32	854	848	92
T-cell lymphoma	397	0	299	280	25
Hodgkin lymphoma	524	0	396	345	31
MCL	315	0	270	261	34
MZL	493	14	371	367	69
Other B-cell lymphomas	593	2	459	448	34
Chronic lymphocytic leukemia (CLL)	1311	10	153	119	44
Other Non-Hodgkin lymphoma	186	1	145	137	7

Meet Your Patient Advocates!

Ben Haines

In March of 1997, when my wife and I were 31, she was diagnosed with 'incurable' stage IVb lymphoma. Devastating news, but thanks to the lymphoma doctors in this very Lymphoma SPORE she is alive and well today. That is all the motivation I need to give back with advocacy. My favorite part of being an advocate is working alongside the doctors; before it always seemed like a 'black box' but now I know they are working tirelessly with the NCI, each other, and other hematologists around the world, collaborating, saving lives, and working for better treatments in the future. We reside in Minneapolis, Minnesota, and adopted a girl from Ukraine, now 12, and have two dogs. Lymphoma is a word, not a sentence.

Bob Paschke

I am a 5 time survivor of Hodgkin's Lymphoma. After my Hodgkin's returned shortly after my bone marrow transplant, I was given a pretty grim prognosis. However, thanks to new breakthrough drugs on clinical trials, the support of others, and God's Amazing Grace, I have been having a great life with lasting remissions with minimal side-affects.

I have been involved in the Cancer Community since my diagnosis and have been very involved in the Lymphoma Research Foundation. I got involved in SPORE just recently in 2015. I think it is very important to support the core research that will inspire the next generation of breakthrough treatments. I have found that the best way to fight this terrible disease is to get involved and help others.

Personally, I love spending time with my three kids and wife. We enjoy traveling and going to lots of soccer and football games.

Lorraine Dorfman

I have been the University of Iowa patient advocate since the inception of the SPORE grant, which began shortly after my husband Donald died of the disease after a 14 year battle. Although I knew that I could no longer help Don, I hoped I could help others with lymphoma. I have enjoyed my association with the SPORE for many reasons: the feeling that I am part of the lymphoma effort; the rewards of learning about the many accomplishments of the researchers and clinicians participating in the project; and helping the SPORE in any way that I can. If you or your family members would like to contact me personally, please feel free to do so at lorraine-dorfman@uiowa.edu. In terms of my personal background, I am professor emerita in the School of Social Work and interdisciplinary Aging Studies Program at the University of Iowa, where for many years I specialized in teaching and research in the field of aging. I have two grown children and two grandchildren, who are a great joy to me. I enjoy travel, reading, gardening, community activities, and am a yoga enthusiast.

Research Support

As patient advocates for the UI/MC Lymphoma SPORE, we have seen personally how the SPORE team is contributing to progress against lymphoma. We, and the other members of the UI/MC Lymphoma SPORE team, are grateful to the National Cancer Institute for ongoing federal support of our collaborative research program. However, cancer research funding by the government is under considerable budgetary stress and is not adequate to support all of the lymphoma research being conducted and planned by the SPORE team. Without private support, some promising lymphoma research projects cannot be pursued. To learn more about how private support helps strengthen the research being conducted through the SPORE, please go to www.uifoundation.org or contact Sarah Russett from the University of Iowa Foundation at sarah-russett@uiowa.edu

Thank you—Ben Haines, Lorraine Dorfman, and Bob Paschke: Patient Advocates University of Iowa/Mayo Clinic SPORE

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 can utilize, and they enjoy hearing from you and helping out as they are able. If you would like more information about the patient advocated in your area you may contact the University of Iowa at 800-237-1225 or the Mayo Clinic at 800-610-7093.

New Funding From the National Cancer Institute to Study Lymphoma Survivorship

LEO Lymphoma Epidemiology of Outcomes

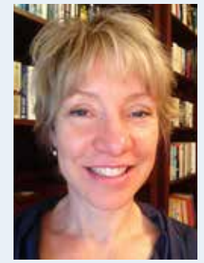
Building from the great success of the Molecular Epidemiology Resource (MER) of the SPORE, we decided to apply for a grant from the National Cancer Institute to expand the MER cohort to more regions in the United States. In May, we heard that we will be funded to expand to six new centers over the next 5 years, which will increase the size of the cohort from 5,000 to over 12,000 lymphoma patients. The new cohort will be called “LEO” which stands for Lymphoma Epidemiology of Outcomes. The goal of the cohort study will be to identify factors that improve lymphoma survivors' length of life and quality-of-life.

Besides Mayo Clinic and the University of Iowa, new institutions include Emory University/Grady Health System in Atlanta, Georgia; MD Anderson Cancer Center in Houston, Texas; Cornell University in New York, New York; the University of Miami Health System/Jackson Memorial Hospital in Miami, Florida; University of Rochester Medical Center in Rochester, New York; and Washington University in St Louis, Missouri. Drs. James Cerhan (Mayo) and Chris Flowers (Emory) are Co-Principal Investigators and Drs. Brian Link (Iowa) and Thomas Habermann (Mayo) are co-Leaders of the Clinical Core. Dr. Andrew Feldman (Mayo) will lead the Pathology Core, and Dr. Susan Slager (Mayo) will lead the Biostatistics and Bioinformatics. Drs. George Weiner and Thomas Witzig will serve on the Steering Committee.

We held our “kick-off” meeting in Atlanta in July – over 50 people who work on the study attended, including study coordinators, physicians, pathologists, epidemiologists, and biostatisticians. We also picked a logo for LEO which you see in this newsletter!

Biostatistics/Bioinformatics Core

The Biostatistics and Bioinformatics Core is directed by Drs. Brian Smith, Terry Braun, and Susan Slager. The Core provides statistical and informatics support for the University of Iowa/Mayo Clinic SPORE projects, developmental projects, and the other cores. It also actively collaborates with and supports the Molecular Epidemiologic Resource. Core members develop study design and data analysis plans for projects initiated in the SPORE, analyze study data, perform data management for each of the clinical trials, monitor adverse events in collaboration with the Clinical Research Core, and prepare data summaries for publication. Bioinformatics expertise is provided and includes custom development of algorithms, software, machine learning, databases, interfaces, and web-based programs. Recent activities include: i) the development and execution of a next-generation sequencing pipeline to analyze DNA samples from cancer patients, ii) the development of web-based forms for the entry of clinical and diagnostic data to support clinical and molecular studies, and iii) integrating PET and CT imaging data with clinical and treatment data to help predict clinical outcomes.



Dr. Susan L. Slager
Mayo Clinic

Dr. Terry Braun
University of Iowa

Dr. Brian Smith
University of Iowa

Clinical Research Core

The Clinical Research Core, co-chaired by Drs. Thomas Habermann and Brian Link, is important because it has the dual function of partnering with the Molecular Epidemiology Research (MER) project which follows patients for outcomes and the Clinical Research Core coordinates the clinical trial programs for the SPORE. There are now 6,952 patients enrolled and in follow-up. Since the last grant cycle, new collaborations in the United States with institutions such as the University of Arizona, Roswell Park and other institutions have been established to complement previous collaborations such as the Dana Farber Cancer Institute and The Broad Institute. New international collaborations have been established with institutions in France, Sweden, and Italy. In addition, the MER has contributed to genome wide association studies through other study groups such as InterLymph which include institutions world-wide. The breadth of these collaborations in the field is unprecedented and moves observations forward at a very rapid pace.

A unique aspect of this program is that patients are followed after their initial clinical evaluation and consent to provide a peripheral blood sample, utilize tissue for research and responses to multiple questions in a booklet are used to study multiple patient background issues that often include the use of the samples from the peripheral blood. Multiple genetic studies have helped advance the science of lymphoma, by contributing to large genome wide association studies (GWAS) in Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia, and other lymphoproliferative disorders.

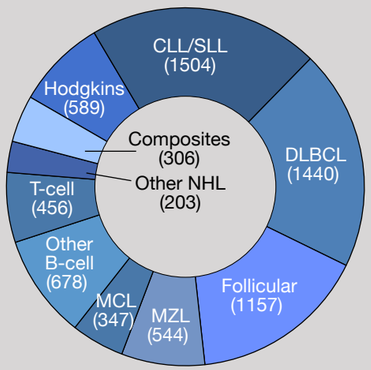
Dr. Thomas Habermann
Mayo Clinic Cancer Center

Dr. Brian Link
University of Iowa
Holden Comprehensive Cancer Center

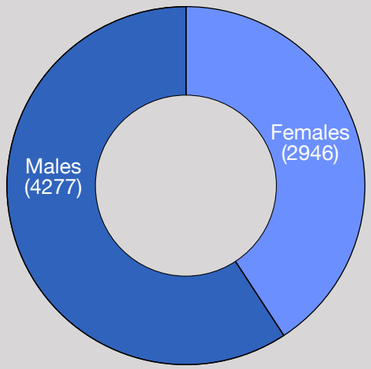
Variations in genes in several pathways in lymphoma have been reported and are under further evaluation.

The Clinical Research Core’s extensive patient data base has allowed for new and unique clinical observations and a number of studies not otherwise possible, which directly helps patients. Over 87 papers have been published over the last four years. For example, a personalized risk prediction model for DLBCL patients alive and disease free after 24 months; the QxCalculate clinical calculator phone app which is available free (www.qxmd.com) which predicts the chances of being alive and event free at the time of the initial presentation. The many investigators in the SPORE grant are most grateful to our patients for participating.

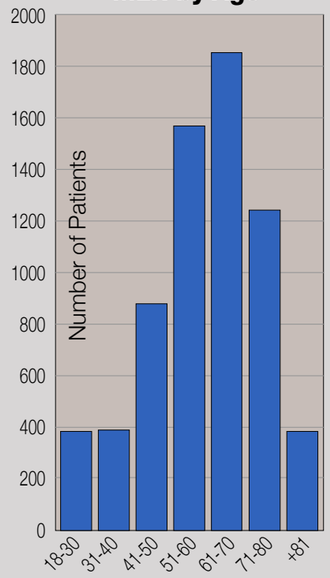
NHL Subtypes



MER by Gender



MER by Age



SPORE Registry Update & FAQ

Many participants have several questions about this project throughout the consenting process and during the follow-up interviews. Below, you will find some of the most frequently asked questions. Answers have been provided by the research team.

If I get my care done at another hospital can I still participate?
Yes! There are many participants who are a part of the registry that do not return consistently to the University of Iowa or Mayo Clinic for their care. We have practices in place to assure your continued participation in the study. One example of how distant participation occurs is our follow-up questionnaire. Completion of follow-up forms not only strengthens our data, it also allows us to keep in contact with you if you receive care at an outside hospital or clinic. The information collected in the follow-up questionnaires is critical to the research we are conducting.

Can I receive the mailed follow-up questionnaires electronically?
Unfortunately, at this time we cannot send the follow-up questionnaires electronically. We are beginning the process to discover electronic formats and programs that could be used to send follow-ups via email or through medical record communication (i.e. MyChart or Patient Portal). It is our hope that in the near future we can offer enrolled participants the ability to receive the follow-up questionnaires electronically. Follow-up questionnaires are sent twice a year to participants during the first three years of enrollment, then annually thereafter.

What is being done with my blood that is collected and stored?
The samples collected are being used to study new tumor/disease markers that might shed light on why one gets lymphoma, why someone responds or does not respond to a specific treatment and predictions on how one will react to their disease in general. As cancer research continues, new markers are frequently being discovered. By keeping a portion of your blood in storage, it allows us to study new markers as they are discovered.
We update the status of all participants' disease, including how the lymphoma responded to specific treatments, in the clinical database so we can answer important questions related to the value of a new marker. The research team greatly appreciates your willingness to provide the samples.

I recently had blood drawn at another facility; can I have them send you some of that blood for your project?
We cannot use any samples that are drawn as routine care from other hospitals or clinics. The blood and tissue that is collected for this study needs to be whole and pure to assure that future testing will be done accurately. We also need the blood to be collected in specific research tubes. It is important in research to use consistent standard procedures throughout the span of the study. We try to be flexible with blood collections and coordinate the draw with your normal clinic appointments at the University of Iowa or Mayo Clinic in Rochester whenever possible.

Do I need to come back to Mayo Clinic or The University of Iowa for research appointments?
No. This is an observational study, which means we will follow you through questionnaires, phone calls and at times, in person when you are being seen for routine care.

Who is we/the research team?
The lymphoma SPORE/MER research team consists of investigators, study coordinators, lab technicians, pathologists, statisticians, clinicians, patient advocates and students who all work together to collect, store, and analyze data and specimens. The University of Iowa and Mayo Clinic research teams work closely together to assure the continued success of the MER.

Thank you for your participation
We want to express our sincere appreciation to you for participating in this study, and for being willing to share your information and samples of your blood. It is only through your generosity that we are able to study new aspects of these diseases and publish our results, such as in the examples below. 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 you may have many questions. Please feel free to contact us at any time and we would be happy to answer any question you may have. University of Iowa: 800-237-1225; Mayo Clinic: 800-610-7093.

MER Publication Spotlight

Carrie Thompson, MD, et al published an article in the journal *Blood* titled "Quality of life at diagnosis independently predicts survival in patients with aggressive lymphoma". A description of the findings from this study follows. Watch Dr. Thompson discussing these results on YouTube:
https://www.youtube.com/watch?v=A95oSi2Dj50#t=125

The purpose of this study was to observe whether quality of life (QOL) measured at diagnosis of lymphoma, through completed questionnaires, can predict survival among patients with aggressive lymphoma enrolled in MER. QOL is a broad term that includes physical, social/family, emotional, and functional well-being. We measured QOL at time of enrollment in MER. We considered "aggressive lymphoma" to include the subtypes diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) grade III, mantle cell lymphoma, T-cell and other high grade lymphomas. There were 701 patients with aggressive lymphoma who completed a quality of life questionnaire at enrollment into the study from 2002-2011. We found that baseline QOL can predict overall survival and event-free survival. Patients with a lower QOL score had a shorter overall survival timeframe than those who reported better quality of life based on the questionnaire. This study provided evidence that measuring quality of life in patients is just as important as other already defined and accepted tools to predict outcome at diagnosis of lymphoma.

A few recent MER publications:

1. Correia C, Schneider PA, Dai H, et al. BCL2 mutations are associated with increased risk of transformation and shortened survival in follicular lymphoma. *Blood* 2015;125:658-67. PMCID: PMC4304111.
2. Novak AJ, Asmann YW, Maurer MJ, et al. Whole-exome analysis reveals novel somatic genomic alterations associated with outcome in immunochemothera py-treated diffuse large B-cell lymphoma. *Blood Cancer J* 2015;5:e346. PMCID: PMC4558593
3. Wudhikarn K, Smith BJ, Button AM, et al. Relationships between chemotherapy, chemotherapy dose intensity and outcomes of follicular lymphoma in the immunochemotherapy era: A report from the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource. *Leuk Lymphoma* 2015 Feb 9 [Epub ahead of print].
4. Ghesquieres H, Slager SL, Jardin F, et al. A Genome-wide Association Study of Event-free Survival in Diffuse Large B-cell Lymphoma Treated with Immunochemotherapy. *J Clin Oncol* (in press).

UIHC MER group

Back row (left to right):
Brian Link, Ashley McCarthy, Jennifer Larson
Front Row (left to right):
Janice Cook-Granroth, Susan Butcher, Umar Farooq

Mayo MER group

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Brian Link, Ashley McCarthy, Jennifer Larson
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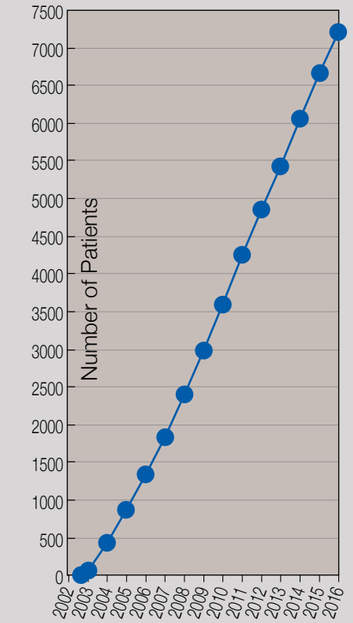
Cummulative Patient Enrollment



MER Accrual by Month