

Research Report

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MANTLE CELL LYMPHOMA SCIENTIFIC WORKSHOP

The 2008 Mantle Cell Lymphoma Consortium (MCLC) Scientific Workshop held in Dallas, TX, brought together 80 of the best and brightest lymphoma researchers from around the world. Investigators reported on their research accomplishments and participants deliberated on translating their progress into improved MCL therapies for the nearly 3,000 U.S. patients diagnosed with MCL each year.

The March 10-11, 2008 meeting was the fifth of its kind since 2003 when the Mantle Cell Lymphoma Initiative began from the urgent need to jump-start research into a disease whose expected survival time once stood at just three years. In 2005, the MCLC was formed by the Lymphoma Research Foundation's (LRF) MCL grant recipients to promote synergy among themselves and other MCL researchers. The advances presented at this year's meeting demonstrate the immense acceleration in the pace of MCL research driven by LRF initiatives. LRF is the world's leading private source for MCL research funding, having raised over \$22 million in pursuit of a cure.

"Your accomplishments give me tremendous ammunition to grow this organization, which has burgeoned now into 20 chapters across the country, and, in turn, to continue funding your work which promises to save so many lives," said LRF President Suzanne Bliss of the MCLC scientists' cutting-edge contributions to the specialized field.

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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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Several leaders, including MCLC Chairman Michael Williams, MD; LRF Board Chairman Andrew Madoff; and LRF Scientific Advisory Board (SAB) Chairman Richard Fisher, MD, took the opportunity to express their gratitude for the donations that fund this vital research and for the exceptional accomplishments of the MCLC's committed investigators. During the workshop, two new members were elected to the MCLC's executive committee: Elias Campo, MD, PhD from the Hospital Clinic, University of Barcelona, Spain and Brad Kahl, MD from the University of Wisconsin.

Essential questions addressed during the presentations included:

- ◆ How can existing therapies be optimized?
- ◆ What are the most promising new therapeutic strategies for MCL?
- ◆ Which cellular pathways are most relevant to the disease's progression and treatment response?
- ◆ How can novel technologies and biology-based approaches contribute to the understanding of the disease, therapeutic targets, and individualization of patient therapy?
- ◆ What are the most promising therapeutic agents and how may they be optimally utilized?

SCIENTIFIC HIGHLIGHTS

Presentations at the 2008 MCLC Workshop represent some of the most exciting, progressive work being done in MCL research. The work of these MCL investigators spans a gamut of differing, yet potentially complementary, strategies to overcome the disease and improve the lives of patients.

The physicians and scientists of the MCLC are expanding our understanding of MCL biology, including the role of cell proteins, mechanisms of cell signaling, and the importance of genetic characterization.

Researchers are also developing and testing novel methods of inducing cell death (apoptosis) in malignant cells while protecting healthy cells and the patient from the often dangerous and debilitating effects of those treatments.

Although our understanding of MCL has grown markedly, especially in the areas of gene expression and morphology, many questions remain. Several MCL investigators that attended the Workshop are attempting to find the answers to some of these questions by:

- ◆ Identifying improved methods of radioimmunotherapy (RIT) to reduce toxicity and target optimal approaches to individual patients.
- ◆ Creating targeted antibodies designed to attack potential weaknesses of cancer cells.
- ◆ Testing drugs alone and in combination for maximal effectiveness.
- ◆ Exploring creative new approaches, for instance, taking advantage of cell structures such as mitochondrial pores to destroy cancer cells from within.

Although science and scientists are often characterized by the popular image of the breakthrough or eureka moment, most scientific progress is based on persistent, cumulative hard work that builds a body of knowledge eventually leading to improvements. For MCL, this translates to prolonged survival and an improved quality of life.

Highlights from this year's meeting include the following:

- ◆ Diagnostic strategies to identify patients with indolent disease using DNA microarray technology and a “Five Gene Model” to predict a patient’s prognosis allowing physicians to more effectively tailor treatment to each patient’s needs.
- ◆ The ability to identify MCLs “Achilles’ Heel” using an RNA interference library that will allow researchers to ID potential therapeutic targets more rapidly.
- ◆ The study of epigenetics to re-express silenced genes, which could be reawakened strengthening the body’s defenses against cancer.
- ◆ Advances in the understanding of new molecular targets such as the heat shock protein (HSP), enzymes, and a dual target radioimmunotherapy approach.
- ◆ Novel engineering methods to transfer “central memory T-cells” equipped with chimeric antigen receptors programmed to kill MCL cells as part of stem cell transplant therapies.
- ◆ A variety of innovative therapeutic approaches including the use of triterpenoids and kinase inhibitors as well as new regimens and combinations for familiar drugs like rituximab.

PRESENTATIONS

In five topic-specific sessions, laboratory and clinical scientists reported their progress in unraveling the secrets of MCL, from biological processes to novel therapeutics. There were many noteworthy presentations, each representing a diverse approach to finding a cure. Most presenters were awarded LRF research grants under the MCL Initiative. However, over the past five years,

they have been joined by an increasing number of others interested in MCL research. This very special group of investigators finds participation in the MCL Workshop to be an invigorating experience that allows them a rare opportunity to share ideas and make connections with their fellows.

Sessions were moderated by MCLC leadership, including:

- ◆ Michael Williams, MD (University of Virginia School of Medicine) - Chairman of MCLC
- ◆ Joseph Connors, MD, FRCPC (British Columbia Cancer Agency)
- ◆ Martin Dreyling, MD, PD (University of Munich-Grosshadern)
- ◆ John Leonard, MD (Cornell University, Weill Medical College)
- ◆ Owen O’Connor, MD, PhD (Columbia University) *Unable to attend workshop.*



MCL Consortium Chairman Dr. Michael Williams (University of Virginia School of Medicine)

Session I: Biology of MCL

*Session Chair – Joseph Connors, MD, FRCPC
(British Columbia Cancer Agency)*

Researchers are examining potential prognostic markers, including cell components responsible for driving proliferation of MCL cells that could point the way to effective, individualized treatment strategies.

Elias Campo, MD, PhD, (University of Barcelona) is developing methods to molecularly distinguish patients with conventional MCL (cMCL) from those with indolent or slow-developing MCL (iMCL) who may not need immediate intensive therapy. Clinically, 10 of the 12 iMCL patients studied had no or very small isolated lymph nodes whereas all 15 cMCL patients presented with lymphadenopathy with only one patient presenting with localized disease. Using a 100K SNP array, a tool to examine DNA from peripheral blood tumor cells, Dr. Campo found that indolent patients have a very high rate of IgVH gene hypermutations and a lack of genomic complexity. Only 3 (20%) of the 15 patients labeled as cMCL had a high load of IgVH gene hypermutations and 13 of them also had two or more chromosomal alterations. The non-nodal indolent disease Dr. Campo describes may represent a subset of MCL patients that do not require immediate anti-neoplastic therapy.

Sandeep Dave, MD, MS, (Duke University) is looking at how microRNAs (molecules that regulate the expression of RNA, genetic material similar to DNA) are turned on and off in both normal and malignant B-cells. These microRNAs have an important role in both cellular differentiation and cancer development. His finding that specific microRNAs are turned on or off at various

stages of B-cell development could help distinguish different types of lymphoma and could be developed into a tool for diagnosing MCL as well as predicting its prognosis.

Little is known about factors that predict survival after MCL diagnosis. **Thomas M. Habermann, MD**, (Mayo Clinic) discussed his team's MCL survival study which identified patients' genes that predict survival with greater acuity than the standard clinical and demographic factors. Using peripheral blood collected from lymphoma patients since 2002 or buccal smears, cells painlessly taken from inside the mouth, in patients in a SEER (Surveillance, Epidemiology, and End Results) population study, the research team aims to use advanced genetic and pathway analysis to further identify genes and tissue characteristics that will improve prediction of MCL outcomes and, ultimately, patient survival.

Andreas Rosenwald, MD, (University of Wurzburg, Germany) discussed identification of a more accurate way to measure the rate of tumor cell division than the widely used chemical marker Ki-67. Researchers zeroed in on five genes (RAN, MYC, TNFRSF10B, POLE2, and SLC29A2) found in MCL tumor samples to create a "proliferation signature" used to predict survival. The signature's ability to measure cancer cell growth was validated in experiments using MCL tissue. With the ability to utilize various tissue samples (either routinely obtained fresh frozen or formalin-fixed, paraffin-embedded tissue specimens), this "Five Gene Model" approach could effectively help clinicians identify appropriate treatment options based on individual prognosis.

A new technology termed "Achilles' Heel" RNA Interference Screens was discussed by **Louis Staudt, MD, PhD** (National Cancer Institute). Using RNA interference, it is possible to inactivate a single gene in a



Dr. Louis Staudt (National Cancer Institute)

cancer cell and thereby determine if that gene is required for proliferation or survival. Dr. Staudt's laboratory has engineered a high-throughput RNA interference procedure which allows them to determine the function of thousands of genes in a single experiment. To date, Dr. Staudt has successfully expanded his RNA interference library to over 10,000 RNA sequences. These pathways are called the "Achilles' heel" of MCL because they are essential for the cell's malignant behavior. Once identified, they can be used as targets for therapy. Dr. Staudt has successfully identified several RNA sequences that block the proliferation or survival of MCL cells. His research team is currently validating the results and applying the screen to new MCL cell lines in hopes of uncovering new proliferation and survival pathways.

Session II: Biology of MCL

*Session Chair – Michael Williams, MD
(University of Virginia School of Medicine)*

Investigators are homing in on the biological components of MCL cells to identify next-generation therapeutic targets and develop improved diagnostic tests.

Harvey A. Greisman, MD, PhD, (University of Washington) presented a new, molecular assay called Translocation-CGH (TGH) which tests for the specific chromosomal rearrangement, also known as the t(11;14) translocation, found in virtually all MCL patients. CGH, or comparative genomic hybridization, is a convenient and powerful way to identify abnormal regions of chromosomes as long as chromosomal gains or losses are even. Dr. Greisman's modification to CGH can detect uneven abnormalities, such as t(11;14). The assay is expected to improve MCL diagnosis by its wider applicability, improved precision, and its sensitivity over existing tests. In addition, TGH may be used to detect translocations and genomic imbalances in other B-cell lymphomas and myeloma.

Daniel Medina, PhD, (Cancer Institute of New Jersey) presented his team's findings on the role of bone marrow stromal cells, B-cell activating factor (BAFF), and MCL cell survival and drug resistance. BAFF, produced by stromal cells and found in the microenvironment of B-cells, induces growth, differentiation, and cell survival (inhibition of apoptosis). BAFF does not differentiate between malignant and benign B-cells and, in effect, protects MCL cells from apoptosis. Dr. Medina demonstrated that BAFF extends the life of MCL cells by increasing the expression of transcription factor NF- κ B. More importantly, he gave evidence that BAFF and stromal cells have a role in MCL drug resistance, a clue to the development of novel therapeutics that could target the interaction between MCL cells and their microenvironment.

Ari Melnick, MD, (Weill Medical College of Cornell University) is focusing on changes in gene expression (epigenetics) and how these differences may contribute to MCL's resistance to current therapies. Silenced or



Dr. Ari Melnick (Weill Medical College of Cornell University)

hypermethylated genes are responsible for drug resistance in MCL. Dr. Melnick's hypothesis is that these genes, when treated with specific biological agents, are "re-expressed", or turned on, thereby allowing a clinical benefit to drugs such as bortezomib. Treating bortezomib-resistant MCL cell lines with the drug decitabine reduced their viability, suggesting that epigenetically silenced genes were in fact re-expressed. The next step is to determine which genes were re-expressed making MCL cells more susceptible to bortezomib. Studying different combinations of drugs like bortezomib and decitabine will eventually lead to clinical trials for the treatment of bortezomib-resistant MCL patients.

Cyclin D1 (a growth-promoting protein), regulates normal cell cycle progression, but is over-expressed in nearly all cases of MCL. **Julia Slotta-Huspenina, MD, reporting on behalf of Leticia Quintanilla-Martinez, MD,** (Technical University of Munich, Germany) analyzed the presence and frequency of cyclin D1 mRNA variants in blastoid and classic MCL and correlated them with proliferation rates. Blastoid MCL, the more aggressive form of the disease, for example, was found to express more frequently short 3'UTR deficient cyclin D1 mRNA variant than classic MCL. Although the blastoid variant was associated with

higher proliferation rates when compared to the classic variant, proliferation rates showed no correlation with the expression of 3'UTR deficient cyclin D1 mRNA. Both blastoid and classic MCL have low expression levels of the cyclin D1 beta mRNA splice variant. Drs. Slotta-Huspenina and Quintanilla-Martinez, capitalizing on the "proliferation signature" of cyclin D1 mRNA, hope to identify unique therapeutic pathways in treating both blastoid and classic MCL.

Michael Wang, MD, (MD Anderson Cancer Center) analyzed MCL incidence data from 1975-2004 based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry. Dr. Wang suggested that MCL's incidence has: increased progressively in the 30-year period examined, was significantly higher in men than in women, and was significantly higher in Caucasians than in African Americans and other races.

Session III: Role of New Molecular Targets, Chemotherapy and Antibody Treatment

Session Chair – Michael Williams, MD (University of Virginia School of Medicine)

To improve survival in MCL, scientists are identifying new proteins as potential treatment targets and are continually testing novel drugs and innovative combinations of new and existing anti-tumor agents.

From the team of Dr. Elias Campo, **Patricia Pérez-Galán, PhD,** (University of Barcelona) presented her team's research on the combination of bortezomib and IPI-504, a heat shock protein 90 (HSP90) inhibitor. HSPs allow cancer cells to tolerate hostile environments and exist in high volume in MCL patients, making it an ideal drug target.



Dr. Patricia Pérez-Galán (University of Barcelona)

Using both MCL cell lines and primary cells, Dr. Pérez-Galán demonstrated the toxic effect of IPI-504 on cancer cells as well as its synergistic interaction with bortezomib (by modulating NF- κ B and UPR pathways). Having successfully studied the combination of IPI-504 and bortezomib in vitro with primary cells from MCL patients, her research team is now planning to study the two drugs in mouse models.

Gaël Roué, PhD (University of Barcelona) also from Dr. Campo's team, presented his research on bendamustine (TREANDA) as an antitumor agent in MCL. Bendamustine has been used in lymphoid tumors and breast cancer for over 30 years and is known for high anti-tumor activity, an acceptable toxicity profile, enhanced response rate, and mild side effects. Dr. Roué's aim was to evaluate bendamustine's mode of action and to characterize the factors associated with bendamustine's ability to induce cell death (apoptosis). It was concluded that the drug activates apoptosis through oxidative stress, the generation of p53 dependent and p53 independent triggers of apoptosis, and by signaling the release of apoptosis proteins from within the cell. Bendamustine was effective in the majority of MCL samples, including those with p53 mutations, and worked synergistically when combined with the drug gemcitabine.

Robert Baiocchi, MD, PhD, (Ohio State University) is looking at the enzyme PRMT5 as a potential novel therapeutic target. PRMT5 influences genes controlling tumor suppression and is found at high levels in MCL cell lines and patient samples, but not in resting B lymphocytes or healthy B-cells. It is believed that reducing the levels of PRMT5 decreases MCL growth, arrests the cell cycle, and re-expresses the normally silenced tumor suppressor gene found in the disease. Dr. Baiocchi is considering novel RNA-based strategies to inhibit PRMT5, and his team continues to work to characterize the multiple ways in which to achieve cell death in lymphomas and solid tumors.

Anti-CD20 radioimmunotherapy (RIT) is an important treatment for MCL though little is known about the effect of high levels of circulating anti-CD20 in the body and whether its function may eventually be blocked. **Ajay K. Gopal, MD**, (University of Washington, Fred Hutchinson Cancer Research Center) tested the CD45 protein as an alternate target to CD20 for radiolabeled



Dr. Robert Baiocchi (Ohio State University)

antibodies. His team of scientists set out to test the substitute target after showing that treatment with anti-CD20 could block subsequent antibodies from attaching to the CD20 protein thereby compromising further therapy. In his preclinical work, Dr. Gopal proved that targeting CD45 after rituximab

MCL Scientific Workshop



SAB Chairman Dr. Richard Fisher
(James P. Wilmot Cancer Center)



Dr. Joseph Connors (British Columbia Cancer Agency) and
Dr. Thomas Habermann (Mayo Clinic)



Scientific Panel of Experts



Andy Madoff (LRF Board of Directors, Chairman)



Dr. Martin Dreyling (University of Munich-Grosshadern)



Dr. John Chan (University of Nebraska Medical Center)



Poster Session



Poster Session



Suzanne Bliss (LRF President)

treatment caused MCL to regress whereas repeatedly targeting CD20 after rituximab proved ineffective. These findings will support a clinical trial to evaluate the safety and feasibility of a similar regimen in patients with relapsed or refractory MCL.

Mitchell Smith, MD, PhD, (Fox Chase Cancer Center) conducted a phase II clinical trial in the Eastern Cooperative Oncology Group (ECOG) to determine whether the response duration after four cycles of R-CHOP for previously untreated MCL can be prolonged by radioimmunotherapeutic (RIT) agent 90 Y-ibritumomab tiuxetan (Zevalin). Of the 49 patients with follow-up data that received complete treatment, 27 (55%) had a complete response and 16 (33%) had a partial response. Mean failure-free survival for all 56 patients enrolled in the study as of this report was 27 months and the estimated overall survival at 18 months was 95%. Neutropenia and thrombocytopenia were the most common toxicities after RIT and 22 of 23 patients recovered blood cell counts by week 12. This study indicates that MCL remission after R-CHOP seems to be consolidated by RIT. Though further follow-up is needed, Dr. Smith's R-CHOP + RIT regimen is promising.

Session IV: Transplantation and Cellular Therapy

*Session Chair – Martin Dreyling, MD, PD
(University of Munich-Grosshadern)*

Experts in stem cell transplants are focusing on improving the effectiveness of transplantation while protecting patients from the potentially ravaging toxic effects on their immune systems.

Michael C. Jensen, MD, (City of Hope National Medical Center) tested a novel method of genetically reprogramming the immune system to recognize and eliminate lymphoma cells and prevent relapse after hematopoietic stem cell transplant (HSCT). This immunotherapy approach to treating MCL is thought to improve survival by rebuilding the immune system with genetically engineered T-cell grafts programmed to kill MCL cells. Dr. Jensen is excited to begin work on a clinical trial using grafts of central memory T-cells (a type of T-cell that can recognize foreign invaders from a previous encounter and mount a stronger immune response following a subsequent encounter) following HSCT for patients with MCL.

In a clinical trial, **Issa F. Khouri, MD**, (MD Anderson Cancer Center) studied different risk-adapted transplant strategies for treating MCL after first remission from chemotherapy and in heavily treated patients. Dr. Khouri's team analyzed 123 MCL patients treated with stem cell transplant noting progression free



Dr. Issa Khouri (MD Anderson Cancer Center)

survival, complete response rates, and prognostic factors found in the blood (B2m, LDH). Autologous stem cell transplantation (ASCT) was found most effective after first remission and the addition of rituximab suggests promising long-term survival. Non-myeloablative allogeneic stem cell transplant (NST) was well-tolerated and safe in

patients beyond their first remission and is capable of overcoming chemotherapy resistance and the adverse risk of biological factors. This study supports the decision to treat patients with autologous or allogenic stem cell transplant based on their chemotherapy remission history.

Dissatisfied with current immunotherapies, **Oliver Press, MD, PhD**, (Fred Hutchinson Cancer Research Center) is testing a new “third generation” retroviral-based approach to generate genetically modified T-cells that recognize the CD20 molecule on the surface of lymphoma cells and have a cell death switch, also known as a suicide gene. This gene, iCasp9, once activated by a special drug, causes the lymphoma cell to kill itself through apoptosis. If effective, the combination of CD20 cTCR and activated iCasp9 would destroy lymphoma cells that the engineered T-cells came into contact with. The team at Fred Hutchinson is working on several projects to evaluate the safety of the third generation immunotherapy. They will assess the feasibility of an immunotherapy regimen lacking the suicide gene and eventually conduct a clinical trial with the new approach.



Dr. Oliver Press (Fred Hutchinson Cancer Research Center)

Session V: Novel Therapeutic Approaches

Session Chair – John P. Leonard, MD (Cornell University, Weill Medical College)

Researchers in the United States and Europe are continually testing the effectiveness and toxicity of various anti-MCL agents (singly and in combination) to zero in on the best conventional and novel therapies for improving MCL survival.

Steven H. Bernstein, MD, (University of Rochester Medical Center) is studying the mechanisms by which triterpenoids and parthenolides (molecules found in plants) cause MCL cell lines to die and, in turn, how they can be combined with other active agents against MCL. The triterpenoids bind to proteins of the mitochondria (a cellular structure responsible for energy production) eliciting cell death in several different ways, including the opening of mitochondrial pores, resulting in the generation of small molecules that damage the cell structure. Dr. Bernstein believes that parthenolides function similarly, but affect a different mitochondrial pore. Targeting mitochondrial pores is an interesting novel therapeutic approach to MCL and preliminary data suggests that drugs like bortezomib may even augment triterpenoid-caused cell death. Further work needs to be done to fully understand the mechanism of action for triterpenoids and parthenolides and to validate the hypothesized therapeutic targets.

Martin Dreyling, PD, MD, (University of Munich-Grosshadern) presented an update on current clinical trials conducted by the European MCL Network, a collaboration of clinicians, scientists and pathologists. The Network’s translational approach focuses on developing individualized therapies based on a person’s molecular risk profile and improving outcomes in lymphoma by using

novel molecular-targeted therapies. Dr. Dreyling presented data from various studies, including a randomized phase III clinical trial evaluating rituximab + high dose Ara-C followed by myeloablative consolidation and autologous transplantation which had an estimated 1-year progression free survival of 89%. He also discussed an active study of elderly high-risk patients randomized between 8 cycles of induction R-CHOP or 6 cycles of R-FC (experimental arm) and then treated with rituximab or interferone maintenance. At 12 months, overall survival was measured at 86% and progression-free survival at 79%.

Ronald Levy, MD, (Stanford University) presented a clinical trial of the small molecule R406 that inhibits the Syk kinase, a protein and gene that acts as a signal transmitter and whose abnormal function is associated with malignancy. When the Syk kinase is inhibited, the cellular signaling network needed for B-cells to live is shut down, effectively killing them. Using primary tumor samples, the Stanford team showed that R406 inactivates the Syk kinase, selectively killing B-cell lines. Further studies validated R406's



Dr. Ronald Levy (Stanford University)

ability to inhibit the B-cell receptor's signaling. Dr. Levy is currently participating in a phase I/II clinical trial to evaluate the compound for activity in patients with relapsed and refractory B-cell NHL.

Geoffrey Shapiro, MD, PhD, (Dana-Farber Cancer Institute) presented MCL clinical trials looking at the mechanisms of action of two MCL drugs, PD0332991 and flavopiridol. MCL is characterized by the over-expression of cyclin D1 and enhanced cyclin D-dependent kinase activity. PD0332991 was found to inhibit the cdk4/6 kinases which contribute to cancer cell growth while flavopiridol inhibits cell cycle kinases and cdk9, a kinase associated with the depletion of proteins that prevent cell death. PD0332991 has gone through early clinical trials in which a recommended daily dose of 125 mg, three weeks of every four, was determined. Currently, a multi-center pilot trial involving several consortium investigators is ongoing in patients with advanced MCL. Preliminary data indicate that the drug is causing reduced cdk4/6 activity in tumor cells, assessed by both tumor biopsies and by PET imaging. Dr. Shapiro is developing PD0332991-resistant MCL lines to better understand mechanisms of resistance. Similar trials for flavopiridol previously showed only modest response rates. Because flavopiridol is believed to be biologically active with the potential to induce lymphoma cell death or delay progression, alternative dosing schedules are being developed in new MCL clinical trials. Dr. Shapiro is evaluating the effect of flavopiridol on lymphoma cells in the context of an ongoing clinical trial at the National Cancer Institute.

Michael Wang, MD, (MD Anderson Cancer Center) is investigating whether bortezomib achieves a higher response rate with lower toxicity when used in combination with cyclophosphamide and rituximab, together known as the BRC regimen. The research team's data suggest a synergistic effect of bortezomib, inducing cell death in 92.6% of primary tumor cells studied. Their in vivo study significantly prolonged long-term event-free survival in 70% of the mice studied. BRC provides hope for high response rates,

even in chemotherapy-resistant patients, in planned clinical trials.

The immunomodulator lenalidomide (Len) in combination with rituximab for patients with relapsed/refractory MCL was discussed by **Michael Wang, MD**, and **Jorge Romaguera, MD** (MD Anderson Cancer Center). By combining rituximab's targeting of the CD20 antibody with Len's targeting of the MCL microenvironment, there is early evidence that the combination is both effective and has a favorable toxicity profile. Though the phase II study is incomplete, the overall response rate for treated patients was 70%. The team at MD Anderson finds these results promising and will conduct further evaluation.

POSTER PRESENTATIONS

Tulin Budak-Alpdogan, MD, reported on behalf of **Joseph Bertino, MD** (Both from the Cancer Institute of New Jersey). Dr. Bertino has discovered a way to optimize environmental conditions for the expansion of hematopoietic stem cells from frozen umbilical cord blood samples. Further analysis will determine the engraftment potential of the expanded cord blood stem cells. This discovery is promising as cord blood offers several advantages compared to bone marrow and peripheral blood, including a greater tolerability by the transplant patient.

Judith K. Christman, PhD, (University of Nebraska Medical Center) is comparing different laboratory techniques (CpG Island Arrays vs. Affymetrix Human Promotor 1.0R Arrays) to determine which is most effective at detecting DNA methylation in MCL and provide evidence that accurately measuring DNA methylation is important because it can



Observing research data at poster session

be used to predict a patient's overall survival. She also reported results on behalf of

Timothy C. Greiner, MD, (University of Nebraska Medical Center) who discovered that four key proliferation signature genes (ASPM, CDC2, TUBA3, and CENPF) were not uniformly decreased by activating control genes with the demethylation protocols studied.

Sophie Dessureault, MD, PhD, (H. Lee Moffitt Cancer Center & Research Institute) is recruiting participants for a phase II trial which is testing the vaccination of cancer patients with autologous tumor cells and GM.CD40L (granulocyte macrophage CD40L expressing) bystander cells. It is too early to evaluate the impact of the vaccine on patients with MCL, but preliminary results of those that have received the vaccine are promising.

Pedro Jares, PhD, (University of Barcelona, Spain) is identifying potential tumor suppressor genes in MCL using a laboratory technique called GINI (gene identification by nonsense-mediated decay inhibition). To date, nine genes have been identified and selected for further analysis. These genes could be new targets for MCL therapies.

Shantaram S. Joshi, PhD, (University of Nebraska Medical Center) is studying ways to reduce minimal residual disease (MRD) in

MCL – disease that is undetectable by conventional methods. Dr. Joshi has shown, in mouse models, that adoptive T-cell therapy with MCL-specific T-cells (a process that involves activating, expanding and modifying T-cells so that they can recognize and attack MCL cells) is effective in the treatment of MRD. Combining MCL-specific T-cells with high dose therapy and other treatments, such as bortezomib, resulted in larger increases in survival and decreased tumor burden.

Timothy McKeithan, MD, PhD, (University of Nebraska Medical Center) is identifying genes that are essential for the survival of MCL by blocking them (through a technique called RNA interference) and observing whether this action kills the cells or prevents their growth. Dr. McKeithan hopes to test all the genes expressed in MCL by using a library of synthetic siRNAs (small interfering RNAs) which targets approximately 22,000 genes. This analysis will lead to the identification of potential therapeutic targets for MCL.

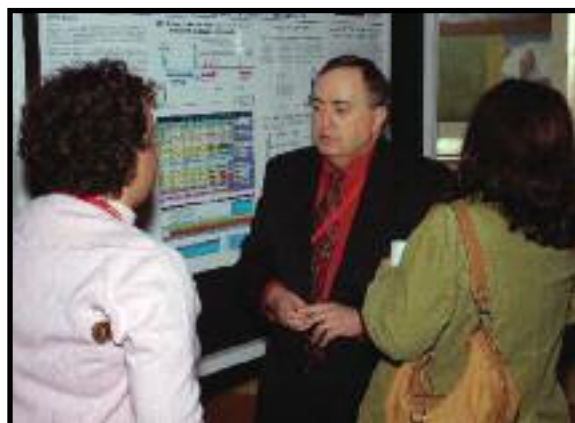
Martin Dreyling, PD, MD, (University of Munich-Grosshadern) reported on behalf of **Christiane Pott, MD** (University Hospital Schleswig-Holstein, Kiel, Germany). Dr. Pott is trying to improve the way minimal residual disease (MRD) is monitored and quantified by using a more sensitive laboratory technique (6-color flow cytometry). A more precise test would provide a faster method of detecting MRD and better individualized patient management.

Mark Raffield, MD, (National Cancer Institute) is investigating the efficacy of the molecule Nutlin-3 in the treatment of MCL. Dr. Raffield discovered that treating certain MCL cell lines with Nutlin-3 or Nutlin-3 in combination with doxorubicin or bortezomib resulted in a decrease in the viability of cancer cells suggesting that it could be used as a potential cancer treatment pending further study.

Amareshwar Singh, PhD, MBA, (Northwestern University) is studying the effect of all-trans retinoic acid (ATRC) and arsenic on MCL survival. It was discovered that both agents induce cancer cell death via different pathways. However, further investigation is required to fully understand the effects of these two agents.

Wendy Stock, MD, (University of Chicago) is evaluating two novel approaches to eliminate minimal residual disease (MRD) during MCL treatment: 1) testing the addition of bortezomib maintenance therapy following autologous stem cell transplant for patients with previously untreated MCL and, 2) testing whether small peptides can be used to eradicate MRD. The first initiative is still recruiting participants. Preliminary data for the second approach has demonstrated that two peptides (RXL and p21) induce cell death in one of the MCL cell lines (MO 1094).

David T. Yang, MD, (University of Wisconsin) is investigating the function of the NF-kB pathway (a molecular pathway that plays a role in the development of MCL). Dr. Yang discovered that bortezomib-resistant NF-kB activity is present in the majority of MCL patient samples and MCL cell lines studied. However, he also discovered that combining bortezomib with an agent that suppresses the resistant pathway (perillyl alcohol) can impede MCL development.



Sharing findings at poster session

SUMMARY

The Mantle Cell Lymphoma Consortium (MCLC) has made tremendous strides toward improving MCL diagnosis, treatment and maintenance. Its success could not have been achieved without the dedication of its members and their scientific contributions. The MCL Workshop gave Consortium members an opportunity to share these achievements and learn from their colleagues in hopes of gaining a greater understanding of the disease.

Despite the scientific advances that have been made, MCL still remains an incurable disease. However, researchers are getting closer to finding a solution with each discovery. By funding research that focuses on different aspects of the disease (such as, understanding the biological pathways that are vital to MCL development, discovering ways to improve current therapies, and conducting clinical trials of novel treatments) LRF and the Consortium are creating a comprehensive picture of MCL and bringing us closer to a cure.

The success of the MCLC has made it a model for the development of additional LRF lymphoma-specific initiatives, including the Follicular Lymphoma and CLL/SLL Initiatives. To date, LRF has formed a Follicular Lymphoma Consortium and a CLL/SLL Committee that will function in similar ways to the MCLC. Over the next few years, LRF will build upon these initiatives, continue to fund promising research projects, and host additional workshops to foster collaboration and accelerate discoveries in these fields of lymphoma. LRF is looking forward to achieving as much success with these new initiatives as it has with MCL.

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