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RESEARCH REPORT

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LRF MANTLE CELL LYMPHOMA REPORT

Mantle Cell Lymphoma

An "orphan" disease receives much needed attention

Mantle Cell Lymphoma is a B cell lymphoma that gets its name because the tumors in the cancer are composed of cells that resemble cells in the "mantle zone" of lymph nodes. It accounts for about 6% of all non-Hodgkin's lymphoma leading to about 3000 to 4000 cases per year in the U. S. To learn more about Mantle Cell Lymphoma turn to page 11 for an excerpt from LRF's soon to be published fact on the topic.

A STAND STILL. Over the last few years there has been substantial progress in the treatment of other forms of lymphoma, but patients with MCL have not benefited significantly from these advances. Clinically MCL has been a frustrating experience for oncologists who fully expect that with more research in the area, patients will find their lives extended while maintaining their quality of life.

A JUMP START. There are several reasons for this slow progress. One has been the lack of good animal models for this disease. And no large phase II/III clinical trials for MCL patients have been performed because of the relative rarity of this type of lymphoma. To address these problems the Lymphoma Research Foundation has established a special research initiative focused on MCL. This effort was made possible by an extremely generous gift (from a donor who prefers to remain anonymous). The donation allowed the Lymphoma Research Foundation to establish a special research initiative focused on Mantle Cell Lymphoma (MCL).

KNOWLEDGE IS THE FOUNDATION. The Initiative's objectives are to → support a spectrum of new research, from the basic understanding of MCL to development of new treatments; → maximize the value

and effectiveness of our MCL research and → bring patients with MCL into active clinical programs. In the first round of funding, this Initiative has provided 3 years of support for 17 research programs at prestigious institutions in the United States, Canada and Europe. In a second round of funding, another 7 projects were selected to start in Fall 2005. For a listing of these new projects, please see page 6. These cutting-edge research projects include both **clinical studies** (improvements and new approaches to chemotherapy, antibody therapy, vaccines and stem cell transplantation) and **laboratory studies** (aimed at discovering the genetic and cellular basis for MCL, thus leading to new treatment targets).

BRING IT ALL TOGETHER. The 2nd MCL Research Workshop was held January 12-13, 2005 in New York City. It provided an opportunity for investigators working on MCL to report on their first year of progress, discuss the current state of the art in Mantle Cell Lymphoma research and treatment, and identify the directions this research should focus on in the future.

ADVANCES. The Mantle Cell Lymphoma Workshop certainly provided evidence that important progress is being made in reaching LRF's goals. New pre-clinical models including both MCL cell lines and animal

models have been established. Progress is being made in better defining the disease in terms of its genetic and biochemical properties. Understanding the cellular factors important for disease initiation and progression are leading to new selective therapies. Clinical trials of novel chemotherapies, immuno-therapies, vaccines and transplant therapies are in progress with some of them showing effectiveness with low toxicity.

PULLING TOGETHER. Another aim of the program is the creation of the Mantle Cell Lymphoma Consortium. The Consortium is a collaborative group consisting of many sites around the world that are working together on studies of this disease. Together they maximize the value of their expertise and the resources they bring to the study of MCL.

The Consortium was initiated at the January 2005 MCL Workshop. Thirty-five investigators immediately joined the group. Since then the Consortium has developed a plan of action that includes several elements. The MCL Consortium action plan includes the following:

- ◆ Creation of a website that will allow researchers to share information and ideas as well as list resources developed by the Consortium for the benefit of all members. For instance, the Consortium plans to develop a cell bank.
- ◆ The Cell Bank would house cell lines that are essential as research tools. Cell lines epitomize different strains of lymphoma and may also represent various sub-populations of lymphoma, in this case, MCL patients (i.e. male vs. female, young vs. old, etc.). By maintaining a source of well-characterized cell lines, the consortium will help its members pursue fundamental research in potential medications and into the key characteristics of various strains of MCL.

- ◆ The Consortium is also planning to pursue Clinical Trials in two forms: a. pilot grants for novel phase I clinical trials and b. multi-center studies designed to broaden patient pools and take advantage of the strengths of collaboration.

- ◆ Another core area that the Consortium plans to address is the development of biomarker data that can support the work of the Clinical Trials. By analyzing tissue samples from patients for biomarkers such as regulators of cell cycles, cell proliferation or cell death, researchers will build a body of knowledge that can be translated into patient treatment. Biomarkers will be

correlated with patient characteristics such as response to various treatments. The results may lead to improved therapy for individual patients and may help lead to novel treatment approaches.

Grants have been received from The Picower Foundation and from a second anonymous donor



Members of the LRF Scientific Advisory Board: Drs. Joseph Connors; Julie Vose; Joseph Bertino and Morton Coleman. The SAB provides scientific leadership to the LRF and these members helped to make the MCL Initiative Research workshop a success.

family, which will help to make the Consortium's plans a reality. The Lymphoma Research Foundation is grateful to the generous donors who have helped to make the Mantle Cell Lymphoma Initiative and the Mantle Cell Lymphoma Consortium possible. This support has greatly accelerated the scope and progress of MCL research by investigators worldwide, who for the first time are able to work in a comprehensive manner toward the Consortium's aim "To identify effective and curative treatment strategies for mantle cell lymphoma."



Reports of the 2nd MCL Research Workshop January, 2005

Role of Chemotherapy and Antibody Treatment

The first session, **Role of Chemotherapy and Antibody Treatment**, was chaired by **Dr. Morton Coleman**, Weill Medical College, Cornell University.

◆The first speaker, **Dr. Michael Williams** (University of Virginia School of Medicine), described the use of preclinical models including a mouse model and a human mantle cell lymphoma cell line. Both are being used to study the optimization of the monoclonal antibody Rituximab's ability to bind with and lead to synergy with other targeted agents, including other monoclonal antibodies, proteasome inhibitors and cytotoxic agents. Differing responses of leukemic versus tissue and nodal mantle cell compartments are being determined, as are mechanisms of treatment response and resistance.

◆**Dr. Sophie Dessureault** (H. Lee Moffitt Cancer Center) presented an early progress report on a phase II clinical trial of a vaccine for patients with MCL. This vaccine is made by mixing two kinds of cells: 1) bystander cells that secrete GM-CSF, and express the CD40L and 2) some of the patient's own tumor cells. Together, the GM-CSF and CD40L, recruit and activate antigen-presenting cells (dendritic cells). These dendritic cells take the tumor cells injected as part of the vaccine and migrate to lymph nodes where they teach the immune system (T-cells) to recognize and kill lymphoma cells anywhere in the body. She and her colleagues will study the development of anti-tumor immune responses after vaccine treatment. Patients are still being recruited to this trial so it is still too early to present results.

◆The third paper in this session was presented by **Dr. Jia Ruan** (Weill Medical College, Cornell University). It describes the use of anti-angiogenic agents (which starve a tumor of its blood supply) as a maintenance therapy which may control disease over an extended period of time. Efficacy and tolerability are important in this setting given the advanced age of

many MCL patients. To meet this need a low dose oral PEP-C regimen was developed. Preliminary data from this combined therapy showed an 84% response rate (42% complete response) in patients with relapsed MCL with durations of 3 to 42+ months. As a result Dr. Ruan and her associates have designed a Phase II clinical trial of the combination of rituximab, thalidomide, prednisone, etoposide, procarbazine, and cyclophosphamide (RT-PEPC) for patients with relapsed or refractory MCL. This study has been approved and is currently accruing patients.

Novel Therapeutic Approaches

Session II, **Novel Therapeutic Approaches**, was chaired by **Dr. Bruce Cheson**, Georgetown University.

◆The first paper in this session was presented by **Dr. Martin Dreyling** (University Hospital, Munich) and described the role of the European MCL Network in evaluating new therapeutic options and identifying molecular risk factors. The network is comprised of clinical and basic scientists as well as an international pathology panel. Evaluation of different treatment regimens has led to new clinical trials evaluating innovative approaches like proteasome inhibitors in combination with immuno-chemotherapy in MCL. In addition, molecular analyses of patients' samples have identified altered expression of cell cycle regulator genes suggesting future targets for treatment of MCL. This *European MCL Network* will function as a liaison partner organization for the recently established MCL Consortium.

◆**Dr. Geoffrey Shapiro** (Dana-Farber Cancer Institute) is investigating the use of cyclin-dependent kinase (cdk) inhibitors as a treatment for MCL. A hallmark of MCL is a translocation of genetic material between chromosomes 11 and 14. This results in the overproduction of the cdk enzyme. Drugs such as flavopiridal reduce the production or activity of the cyclin-dependent kinases. This slows growth of the cancer cells. These drugs represent a novel therapeutic for MCL with high potential. Dr. Shapiro is studying the effects of cdk inhibitor compounds in MCL cell lines and assessing their synergy with other agents. He and his colleagues are also conducting a phase I trial of flavopiridal in patients with MCL and solid tumors using a different treatment schedule than previously used to maintain sustained concentrations of the drug.

◆ **Dr. John C. Byrd** and his colleagues at Ohio State University are also studying the use of flavopiridal in patients with refractory MCL and Chronic Lymphocytic Leukemia (CLL). A phase I/II study of patients with MCL is being initiated using a novel schedule of drug administration.

◆ **Dr. Owen O'Connor** (Memorial Sloan-Kettering Cancer Center) described the treatment of over 59 patients with relapsed or refractory indolent lymphomas, including 30 patients with MCL, using the proteasome inhibitor bortezomib. A proteasome is a complex of proteins in normal and cancer cells. It plays a critical role in recycling regulatory proteins that govern basic cellular activities including apoptosis, i.e., programmed cell death. For all patients the response rate to the bortezomib regimen was 52%, while MCL patients had a response rate of about 54%. Future trials will focus on integrating bortezomib into a standard chemotherapy-based treatment program. Dr. O'Connor also described the development of a high-throughput cell based screen to identify novel drugs for the treatment of MCL. Using MCL cell lines his laboratory has screened over 20,000 compounds and has obtained promising "hits". They anticipate screening well over 150,000 compounds before year's end.

◆ Treatment of MCL with an mTOR inhibitor was discussed by **Dr. Thomas Witzig** (Mayo Clinic). As described before, MCL is characterized by a chromosomal translocation that results in the overexpression of cyclin D1. The mTOR enzyme regulates the translation of cyclin D1 messenger RNA into cyclin D1 protein. Lowering the production of cyclin D1 slows the growth of MCL cells. Thirty-four patients were enrolled in the study. The overall response to treatment with CCI-779, the mTOR inhibitor, was 38% with one complete response and 12 partial responses. Thus CCI-779 has substantial anti-tumor activity in relapsed MCL and should be further studied.

Transplantation and Cellular Therapy

Session III, **Transplantation and Cellular Therapy**, was chaired by **Dr. Julie Vose**, University of Nebraska Medical Center.

◆ **Dr. Craig Moskowitz** (Memorial Sloan-Kettering Cancer Center) discussed the experience at Sloan-Kettering using high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT) in patients with MCL. Fifty-four patients were treated between 1994 and 2004. Median overall survival of these patients is 69 months. Patients who were transplanted "up front" rather than after relapse had a significantly better progression free survival.

◆ Projects involving high-dose radioimmunotherapy (RIT) in relapsed or refractory MCL were described by **Dr. Ajay Gopal** of the University of Washington. The first project treats adults aged 18 to 59 with myeloablative doses of radioimmunotherapy along with etoposide and cyclophosphamide followed by autologous stem cell transplantation (ASCT). Of 20 patients treated 85% are alive and 55% are progression free. A second project uses high doses of RIT without chemo followed by ASCT to treat patients over the age of 60. Six of 7 patients are alive and 4 of 7 are progression free. A third project, using RIT followed by a mini allogeneic transplant for patients who cannot undergo, or have relapsed after, ASCT, is actively accruing patients. Studies such as these may show that RIT can provide a valuable therapeutic option for patients with relapsed or refractory MCL.

◆ **Dr. Tulin Budak-Alpdogan** (The Cancer Institute of New Jersey) and her colleagues have developed a vector carrying drug resistance genes against methotrexate (MTX) and cytarabine (ara-C). Introduction of these genes into a lymphoma mouse model allowed the mice to be treated with high enough levels of MTX/ara-C to prevent tumor growth in mice carrying the resistance genes. This level of drugs was 100% lethal to mice not carrying the resistance genes. A clinical protocol is planned to test this vector carrying drug resistance in patients with relapsed or resistant MCL.

◆ **Dr. Richard Champlin** (M.D. Anderson Cancer Center) described a project aimed at developing a safer and more effective system of allogeneic transplantation for treatment of MCL. A problem in allogeneic transplantation is the development of graft vs host disease (GVHD) caused by the reaction of the donor immune T cells against recipient tissue. Since T cells are however needed to mediate the graft vs lymphoma (GVL) effect

of the transplant, Dr. Champlin and his associates plan to solve the problem by replacing the T cells with donor cells stimulated against a third unrelated mismatched individual. These T cells will not cause GVHD but will mediate GVL effects.

◆The focus of **Dr. J. N. Cooper's** research at the City of Hope National Medical Center is to combine gene therapy and immunotherapy to treat patients with MCL. To do this his group has developed a DNA plasmid vector carrying a CD19 receptor gene which combines antibody recognition with T cell effector functions. Mouse studies have shown that this approach is feasible and a clinical trial has been designed for patients with refractory/relapsed CD19+ MCL.

◆**Dr. Issa F. Khouri** (M.D. Anderson Cancer Center) described a trial using non-ablative allogenic stem cell transplantation for advanced or recurrent MCL. Eighteen patients were treated in one of two consecutive trials using different conditioning regimes. The conclusion from this study is that the treatment is a safe and potentially effective strategy for patients with relapsed and chemosensitive MCL.

◆Since MCL is characterized by a general resistance to conventional therapies because of the persistence of residual disease, **Dr. Shantaram S. Joshi** and colleagues at the University of Nebraska Medical Center have looked at the development of innovative cellular treatments to eliminate residual lymphoma. One such option is the use of autologous dendritic cell-based therapy. Dendritic cells (DC) are potent antigen-presenting cells that possess immunostimulatory properties. DC were prepared using 3 methods and these showed effectiveness in a mouse model. Further testing will be carried out in MCL cells in culture and the results of these studies will be used to design a Phase I clinical trial to determine the feasibility of DC based immunotherapy in MCL patients.

◆**Dr. Joseph Bertino** presented the paper scheduled to be given by **Dr. Rowayda Peters** (The Cancer Institute of New Jersey), who was delayed in Switzerland. This paper addressed a method of successfully expanding umbilical cord blood cells as a source of hematopoietic progenitors for adult transplantation. Based on the successful results to date, a Phase II clinical trial is planned.

◆**Dr. Roger Strair** described three areas of translational studies (that is, studies linking basic research to clinical treatment) being pursued at The Cancer Institute of New Jersey. The first area explored the use of modified adenovirus to infect and kill MCL cells. The second area of research is exploring the ex vivo conditions that induce stimulatory molecules that facilitate antigen presentation by MCL cells. These conditioned cells would be used as vaccines. The third area of interest is the development of a novel immunotherapy in which patients receive infusions of irradiated donor lymphocytes every 8 weeks with no other treatment. *(Continued on page 8.)*



Mantle Cell Lymphoma Grants

2005 Awards

Tulin Budak-Alpdogan, MD and Joseph Bertino MD; The Cancer Institution of New Jersey, UMDNJ, New Brunswick, NJ; *Post-Transplant High Dose MTX/ARA-C consolidation: A Drug Resistance Gene Transfer Strategy for Myeloprotection*

Joseph Bertino MD and Rowayda Peters, PhD; The Cancer Institute of New Jersey, UMDNJ, New Brunswick, NJ; *Successful Expansion of Umbilical Cord Blood Stem Cells*

Elias Campo, MD, PhD University of Barcelona, Barcelona, Spain and Andreas Rosenwald, MD; University of Wuerzburg, Germany; *Molecular Mechanisms Associated With Clinical Progression and Drug Resistance In MCL*

Elliot Epner, MD, PhD; Oregon Health and Science University, Portland, OR; *Turning Cyclin D1 on and off in mantle cell lymphoma*

Shantaram Joshi, PhD; University of Nebraska Medical Center, Omaha, NE; *Optimizing Dendritic Cell-Based Therapy for Mantle Cell Lymphoma*

Timothy W. McKeithan MD, PhD and John Chan, MD; University of Nebraska Medical Center, Omaha, NE; *Screening with siRNA libraries to identify potential therapeutic targets for MCL*

Louis M Staudt, MD, PhD; National Cancer Institute, Bethesda, MD; *Identification of Therapeutic Targets in Mantle Cell Lymphoma Using an RNA Interference Library Screen*

2004 Awards

Laurence JN Cooper, MD, PhD; City of Hope National Medical Center, CA; *Targeting minimal disease after autologous hematopoietic stem-cell transplant for MCL by adoptive transfer of CD19-specific t-cells*

Sophie Dessureault MD, PhD; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; *Ph I clinical trial using a universal GM-CSF-producing & CD40-L expressing bystander cell line (GM.CD40L) in the formulation of autologous tumor-cell based vaccines for cancer patients with Stage IV disease*

Johannes Drach, MD; University Hospital Vienna, Austria; *Growth control of MCL by the addition of Thalidomide to standard treatment*

Martin Dreyling, MD, PhD & W. Hiddemann, MD, PhD; University Hospital Grosshadern/LMU Munich, Germany; *The European MCL Research Network: Evaluation of new therapeutic options and identification of molecular risk factors*

Timothy C. Greiner, MD; University of Nebraska Medical Center, NE; *Methylation analysis in mantle cell lymphoma using an oligonucleotide microarray*

Owen A. O'Connor, MD, PhD; Memorial Sloan Kettering Cancer Center, NY; *A translational approach for the discovery and evaluation of novel drugs for the treatment of MCL*

Louis M. Staudt, MD, PhD; National Cancer Institute, MD; *Gene expression profiling in MCL*

Roger Strair, MD, PhD; The Cancer Institute of New Jersey, NJ; *Translational research in mantle cell lymphoma*

2003 Awards

Richard E. Champlin, MD; MD Anderson Cancer Center, Houston TX; *Separation of graft vs lymphoma from graft vs host disease using antithird party cytotoxic t-cells (CTL) for treatment of MCL*

Richard J. Ford, MD, PhD; MD Anderson Cancer Center, Houston TX; *Molecular and biological approaches for targeting new therapies in MCL*

Randy D. Gascoyne, MD, FRCPC; British Columbia Cancer Agency, Vancouver, British Columbia, Canada; *New Molecular Targets in Mantle Cell Lymphoma*

Ajay K. Gopal, MD; The University of Washington, Seattle, WA; *High-dose radioimmunotherapy based transplant conditioning regimens for relapsed or refractory MCL*

Issa Khouri, MD; MD Anderson Cancer Center, Houston TX; *Allogeneic stem cell transplantation with Rituximab-containing nonablative conditioning regimen for advanced/recurrent MCL*

John P. Leonard, MD; Weill Medical College of Cornell University, New York, NY; *Angiogenesis and anti-angiogenic therapy in MCL*

Jonathan Said, MD; University of California, Los Angeles, CA; *PIM1 in the pathogenesis of MCL: Functional collaboration with cyclin D1, potential therapeutic target*

Geoffrey I. Shapiro, MD, PhD; Dana Farber Cancer Institute, Boston, MA; *Cyclin-dependent kinase inhibitors in MCL*

Michael E. Williams, MD, FACP; University of Virginia, VA; *Mechanisms of response and resistance to monoclonal antibody therapy in a preclinical model and in patients with MCL*

GLOSSARY OF TERMS

Allotransplant (allogeneic transplant): a transplant of cells, tissue or organ from one individual into another.

Antibody: any of a large number of proteins that are produced by specialized B cells after stimulation by an antigen and act specifically against that antigen in an immune response.

Antigen: a substance that induces the production of antibodies. Examples are foreign proteins and viruses.

Autologous: self-derived. Autologous stem cell transplantation: A type of stem cell or bone marrow transplantation in which a patient receives their own cells.

Biomarker (biological marker): gene or chromosome changes or changes in cellular regulatory proteins that may be associated with a propensity for a particular malignancy or with response to certain therapies.

Cyclin D1: a growth promoting protein that is a sensitive molecular tool for diagnosing MCL.

Immunotherapy: a treatment that uses or stimulates the immune system to fight infection and disease, including cancer.

Lymphatic system: the tissues and organs that store and carry lymphocytes that fight infection and other diseases.

Methylation: addition of a methyl group (a chemical group composed of one carbon and three hydrogen atoms) to a nucleic acid.

Plasmid: a small, independently replicating, circular piece of DNA which can be transferred from one organism to another. Widely used in genetic engineering as vectors (see below) of genes.

Proteasome: a normal cellular machine that breaks down old, worn out, and/or improperly folded proteins.

Radioimmunotherapy: therapy using an antibody that has been linked to a radioactive element.

Stem cell: a cell with daughter cells that may differentiate into other cell types.

Vector: Something which transfers things from one place to another. An example is a plasmid which transfers DNA from one cell to another.

Vaccine: An antigen preparation which when injected will elicit the expansion of responding white blood cells so that immune protection is provided against a disease.

Genetic and Molecular Approaches

The fourth session, **Genetic and Molecular Approaches**, was chaired by Dr. Joseph Bertino (The Cancer Institute of New Jersey).

◆The first paper in this session was given by **Dr. Sandeep Dave**, a member of Dr. Louis M. Staudt's group at the National Cancer Institute. This laboratory is studying gene expression profiling in lymphoma. This is a technology that measures how the activity of certain genes affects the length of survival of MCL patients. This may provide insight into the mechanisms within the cell that influence survival in MCL patients.

◆**Dr. Andreas Rosenwald** and his associates at the University of Würzburg, Germany are studying gene expression profiles. They are, as well, performing comparative hybridization analysis (CGH) on the same MCL specimens. CGH is a technique that allows the comparison of chromosomes from

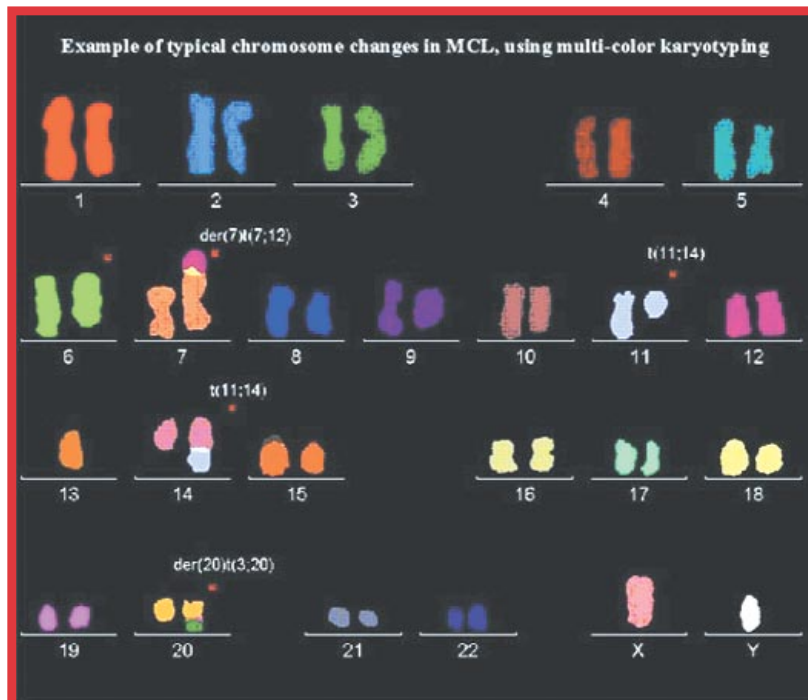
normal tissue to those from cancer cells. This permits investigators to detect changes in chromosomes such as gain or loss of genetic material. Using this technique they have been able to link certain changes with favorable or bad overall survival in MCL. Correlation of the findings of CGH and gene expression profiling may help to identify genes that are critical for the disease process in MCL.

◆In a second project, **Dr. Rosenwald** with **Dr. Elias Campo** at the University of Barcelona are taking a quantitative approach to understand the causes of MCL and the variability in survival of MCL patients. By measuring the expression of a number of genes

associated with the cell division cycle they have found that the degree of tumor cell proliferation is a good predictor of survival for this lymphoma. This information should provide a rationale for the design of therapy for MCL.

◆**Dr. Doug Horsman** (British Columbia Cancer Agency) reported on a project whose purpose is to fully define the chromosomal alterations associated with MCL. MCL, like other cancers, is caused by the accumulation of genetic alterations. When the DNA of mantle cells is examined during cell division by several sensitive assays many alterations at the chromosomal level can be

detected. The detection of similar changes in different MCL patients indicates that these alterations affect the development and course of the disease. Recently new techniques have been developed using special multi-colored fluorescent dyes. These are more sensitive and detect all the major chromosome changes that occur in cancer



Doug Horsman's research project is focused on defining the chromosomal alterations associated with MCL. Above is an example of typical chromosome changes in MCL, using multi-color karyotyping.

cells. This project will examine a large number of cases of MCL to develop a complete picture of the chromosome changes associated with this disease. Correlation of this data with that from gene expression studies will identify changes that play a critical role in disease initiation and progression. This may yield new targets for therapy.

◆**Dr. Carolyn Brown**, an investigator at the University of British Columbia, is trying to determine whether there is a genetic basis for the fact that MCL is found more frequently in males. This is not true for other types of lymphoma. Since females have 2 X chromosomes while males are XY, Dr. Brown is studying the role of

changes in the X chromosome in the development of MCL. To do this she and her colleagues will look at mutations and also at changes in the cell that alter the expression of genes on the X chromosome. When they compared gene expression in samples from 72 men and 19 women with MCL they identified 235 genes that were expressed differently in males and females. Thirteen of these genes were on the X chromosome and 6 were Y-linked. Further study of the changes in these genes is ongoing.

◆The long-term goal of **Dr. Timothy C. Greiner's** (University of Nebraska Medical Center) research is to identify DNA methylation patterns that are important in the MCL disease process. Methylation is one of the processes in the cell that controls which genes are expressed in that cell. Not every gene should be turned on in every cell—the pattern of expression of genes in a cell determines what kind of cell it is. Abnormal methylation patterns are found in many cancers. Dr. Greiner's laboratory will analyze the methylation changes in MCL samples using the microarray technique. This allows the testing of large numbers of genes on a single slide. They have found that three of seven genes that control cell growth and survival are methylated in two-thirds of MCL cases. Using MCL cell lines they will explore whether demethylating agents could enhance chemotherapy.

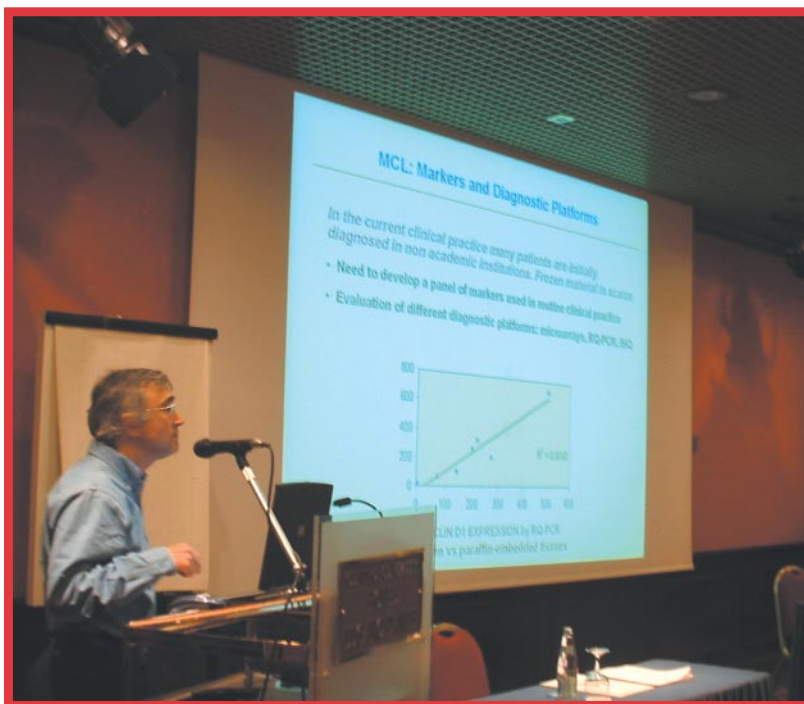
◆**Dr. T.W. McKeithan**, also at the University of Nebraska Medical Center, described the use of small interfering RNAs (siRNAs) to identify possible targets for treating MCL. RNA interference is a naturally occurring phenomenon in cells that scientists are now using to create treatments for disease. RNA

normally consists of a single strand. But double-stranded RNA can be created in the cell by mistake, or viruses entering the cell can create double-stranded RNA. As a defense the cells have a mechanism for destroying double-stranded RNA and any matching single-stranded RNA before a protein can be made. Scientists can manufacture double-stranded RNA whose code sequence corresponds to that of a single-stranded messenger coding a protein causing disease. When this is introduced into a cell, the cell then destroys it and any matching messengers in the cell and shuts off production of the protein. Dr. McKeithan and his colleagues are using siRNAs to study a number of genes suspected of playing a role in MCL and determine which of these candidate genes are, in fact, essential for survival or growth of MCL cells. Identification of these genes will provide novel targets for cancer therapy.

◆**Dr. Richard J. Ford** (M.D. Anderson Cancer Center) focused on the specific signaling pathways that MCL cells use to sustain unregulated growth and extend tumor cell survival. He and his associates have shown that the Tumor Necrosis Factor (TNF) family of growth and survival factors that control lymphoid cell growth do not function normally in non-Hodgkins lymphoma. Specific TNF members are dysregulated in MCL allowing unrestricted tumor growth. These findings provide an

opportunity to develop new therapies that selectively block these TNF family factors. Several novel types of therapy have been designed and are being tested in cell lines and mouse models to see whether they can control the unregulated growth of MCL cells.

◆Several areas of research being carried out in his laboratory were described by **Dr. Jonathan W. Said**



Dr. Elias Campo of the European MCL Network speaks to the MCL Consortium while they gathered for the International Conference on Malignant Lymphoma, June 8 to 11, 2005. This was the Consortium's first opportunity to meet as a group and begin developing plans for action.

(UCLA). One of these is the use of histone deacetylase inhibitors as a treatment for human lymphoid cancers. Two of these inhibitors, suberoylanalide hydroxamic acid (SAHA) and valproic acid were tested in a number of human lymphoid cell lines. All of the cell lines were sensitive to the antiproliferative effects of these agents. In a mouse model SAHA inhibited growth of mantle cell lymphoma without major toxic effect. These agents are promising possible therapies for MCL and related cancers. Another research project in this laboratory focuses on drug resistance. Since drug resistance is a common clinical problem in treating cancer, Dr. Said and his associates have developed a model system to determine how resistance to a new drug, Velcade, might come about. They have generated cell lines resistant to Velcade and are analyzing the mechanisms by which resistance occurs. These findings will be useful for developing new drug combinations to overcome resistance.

◆ **Dr. Leticia Quintanilla-Martinez** (GSF-Research Center for Health and Environment, Nueherberg, Germany) described the development of MCL model cell lines for studying the expression of cyclinD1 and its interaction with other cellular factors that lead to unregulated growth in MCL. Analyzing the factors that affect the cell cycle and being able to manipulate them in these model lines should provide information about the mechanism of MCL development and help design targeted therapies for MCL.

◆ **Dr. Elliott Epner's** research (Oregon Health and Science University) is also focused on cyclin D1. Cyclin D1 is deregulated and overproduced in most patients with MCL. Dr. Epner is studying the genetics and the biochemical interactions in the cell that affect cyclin D1 overexpression. His laboratory is also investigating novel therapeutic agents that down-regulate cyclin D1 in MCL cell lines.

◆ **Dr. Wan Lam** (British Columbia Cancer Agency) is analyzing alterations in the chromosomes in MCL. Although the chromosomal translocation t(11;14) is the hallmark of MCL, it is known that this alone is not sufficient for inducing the cancer. Additional chromosomal aberrations are required for the malignancy. In contrast to other lymphomas in which both chromosome gains and losses occur, MCL is predominately characterized by chromosome loss. Dr. Lam's study aims to identify the genes disrupted in MCL using a special type of microarray. This special assay will allow chromosomal loss or gain to be detected across the entire set of chromosomes (genome) with better

resolution than previous techniques. A series of MCL cell lines have been studied using this technique and the chromosomal locations of recurrent changes have been documented. This genetic data can be compared to gene expression data in the same cell lines. Using these techniques Dr. Lam and his colleagues have identified numerous known and novel regions of genetic alterations in the MCL genomes. This kind of data is crucial to understanding the biology of MCL and to design and develop new treatments for.

Summary

The Mantle Cell Lymphoma Research Workshop succeeded in bringing together and stimulating dialogue among some of the top research scientists in the world who are working on Mantle Cell Lymphoma, including those currently funded by the LRF Mantle Cell Initiative and a few new groups who seek funding. The presentations, which covered the breadth of the research being done on this disease from laboratory studies to the latest clinical trials, allowed these researchers to share and discuss their findings with their scientific peers. The presentations covered a broad range of topics including classic and novel chemotherapies, immunotherapies, vaccines, transplantation and cellular therapies. Basic research studies focused on the genetic and biochemical nature of MCL and suggested possible new targets for therapy. The conference revealed how much progress has been made in the first 18 months of the LRF Mantle Cell Lymphoma Initiative. New pre-clinical models have been established and progress is being made in better defining the genetic and biochemical properties of MCL. Clinical trials of novel chemotherapies, immunotherapies, vaccines and transplant therapies are in progress.

The Workshop highlight was the discussion of clinical trials in mantle cell lymphoma and the formation of the Mantle Cell Lymphoma Consortium, which will increase the pace of MCL research and take the group to an increased level of communication, sharing of data and lab resources, and working together to develop curative treatments for MCL. The clinical studies reported that a total of over 200 patients with mantle cell lymphoma had been recruited into one of the nine clinical trials supported in the LRF Initiative. Early results suggest that the approaches being tested are safe, and early signs of effectiveness were seen; however the entire

target enrollment and follow-up time period is needed to confirm effectiveness.

The MCL Consortium will provide a resource for the scientists to exchange information in a more real-time fashion, to allow them to share in resources

through the cell bank, and to stimulate new clinical trials, to translate the laboratory findings quickly into clinical trials for patients with mantle cell lymphoma. The hope is over the course of the next years to develop and define curative therapies for treating mantle cell lymphoma.

Excerpted from LRF's soon to be published Fact Sheet.

What is Mantle Cell lymphoma?

The term non-Hodgkin's lymphoma (NHL) refers to a group of over 30 closely related cancers that affect the **lymphatic system**. Although all types of NHL have certain characteristics in common, they differ in many ways. They differ in what the cancer cell looks like under a microscope, the cell's molecular features, how the cell grows, and how the tumor affects the body. These differences call for distinct treatment approaches that are best suited to attack each particular form of lymphoma. Each lymphoma type is currently classified according to the normal cell of origin. Since the two main types of lymphocytes are T-lymphocytes and B-lymphocytes, lymphomas are designated as "B-cell" or "T-cell." Mantle cell lymphoma (MCL) is a B-cell lymphoma that gets its name because MCL tumors are composed of cells that resemble cells in the "mantle" zone of lymph nodes. Frequently, MCL tumors are found in many lymph nodes, one or more organs, and bone marrow in patients with the disease, although most patients with MCL have minimal or no symptoms. MCL accounts for a relatively small component (2% to 8%) of all cases of NHL in the United States. This lymphoma often affects older men (over 60), and patients almost always have advanced disease when it is diagnosed.

How is Mantle Cell Lymphoma diagnosed?

To confirm the diagnosis of MCL, doctors will first view a biopsy sample under the microscope, often complementing this step with sensitive molecular tests that detect alterations in the genetic material of tumor cells in the biopsy tissue. Overproduction of a growth-promoting protein called **Cyclin D1** (also called Bcl-1) is found in more than 90% of cases and is considered a very sensitive tool for diagnosing MCL. The overproduction of Cyclin D1 is caused by a molecular event called a genetic translocation, in which inappropriate shuffling of DNA directs cells to make large quantities of this growth-stimulating protein. Other molecular tests may also be used. One-quarter to one-half of MCL patients have higher than normal levels of certain proteins that circulate in blood, such as the enzyme lactate dehydrogenase (LDH) and the protein beta-2 microglobulin. Measuring levels of these proteins can often help gauge how aggressive a tumor is and may guide therapy decisions.



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