

EXTRA! EXTRA!

## HEADLINE OF THE FUTURE

### Generosity Cures CLL; Keating Can Now Retire

**W**e see many major breakthroughs in the press identifying new discoveries in rats and mice or cell lines which will hopefully lead to the cure of cancer. Unfortunately, a vast majority of these discoveries become insignificant over time. In the future, when the headline reads that the president of CLL Global Research Foundation has decided to retire, you will know that “Generosity Cured CLL.” Until that time we will continue to forge ahead.

Many years ago, childhood acute lymphocytic leukemia (ALL) was considered to be a dreaded, universally fatal condition. Then one of our board members, Dr. Emil J Freireich, and his colleagues at the National Cancer Institute researched different treatment combinations to discover the first cures of childhood leukemia. Now the majority of children and many adults with ALL can be cured. However, there remains a small proportion of ALL patients who are not saved.

Can we do the same with CLL, but better? It is obvious that cancer is one of the major problems facing our society. It becomes more prevalent as we age and the “large cancers” seem to be most

“Taking an active role... will benefit everyone impacted by the disease.”

resistant to treatment advances. Rather than taking on cancer in its entirety, we have decided that our primary focus should be to cure one disease - CLL.

CLL Global has the most efficient approach to funding medical research that I have experienced. Generous contributions from patients have enabled CLL Global to set up a cost effective way of funding a highly productive international CLL research team. The CLL community now has an FDA approved frontline treatment regimen which can achieve complete remission in the vast majority of CLL patients who are young and in good physical shape. There are still hurdles to cross for the majority of older patients who have other medical complications. We must focus on getting the right treatment for each patient.

How long will it be until the headline becomes a reality? I predict that strategies will soon be in place to control CLL cell growth, improve immunity and educate the immune system to attack the CLL cells. Fortunately, many CLL patients now live several years. This means that it takes a long period to confirm that new strategies are successful.

How did we get to where we are? It is a result of patients who decided they wanted a say in funding CLL research. The generosity of donors to CLL Global is spectacular. Your support has allowed our Foundation to fund innovative and collaborative research on a global scale. The model of solving the “CLL jigsaw puzzle” is alive and well. Taking an active role in piecing the puzzle together will benefit everyone impacted by this disease. The holiday season is upon us and it is now time to make decisions as to how we can support meaningful causes. CLL Global would be proud to be the recipient of your generosity. Help us write the headlines of the future. ::



Dr. Michael J. Keating



Dr. Michael Keating, Professor of Medicine at MD Anderson Cancer Center, serves as president and CEO of the CLL Global Research Foundation. He is an internationally renowned CLL clinical scientist dedicated to patient care and to development of potentially curative CLL therapies.

### inside this issue:

- 2 Mouse Models “Trap” CLL Genes
- 3 Signal Transduction Inhibitors: A Brand New World
- 4 CLL in the Elderly: Past, Present and Future
- 4 CLL Global Hosts Patient Symposium
- 5 Unscrambling Prognostic Factors in CLL
- 6 Cord Blood May Strike a Match

## SCIENTIFIC ADVISORY BOARD

**Federico Caligaris-Cappio, M.D.**  
Istituto Scientifico San Raffaele, Italy

**Daniel Catovsky M.D., DSc**  
Institute of Cancer Research, UK

**Carlo Croce, M.D.**  
Ohio State University

**Neil Kay, M.D.**  
Mayo Clinic

**Thomas Kipps, M.D., Ph.D.**  
University of California, San Diego

**Raymond Meyn, Ph.D.**  
MD Anderson Cancer Center

**Susan O'Brien, M.D.**  
MD Anderson Cancer Center

**William Plunkett, Ph.D. (chair)**  
MD Anderson Cancer Center

**Kanti Rai, M.D.**  
Long Island Jewish Medical Center

**Steve Rosen, M.D.**  
Northwestern University

**Stephan Stilgenbauer, M.D.**  
University of Ulm, Germany

**William G. Wierda, M.D., Ph.D.**  
MD Anderson Cancer Center

## BOARD OF DIRECTORS

**Phyllis Gordon Cohen**  
Kansas City, MO

**Ted Collins, Jr.**  
Midland, TX

**Emil J Freireich, M.D.**  
Houston, TX

**Louis Katopodis**  
Katy, TX

**Michael J. Keating, M.B., B.S.**  
President & CEO  
Houston, TX

**David Kesterson, Ph.D.**  
Denton, TX

**Susan Berry Kohlhas**  
Glenmoore, PA

**Robert Nichols**  
Dallas, TX

**Martin Raber, M.D.**  
Houston, TX

**B.M. (Mack) Rankin, Jr. (chair)**  
Dallas, TX

## MOUSE MODELS

# "Trap" CLL Genes

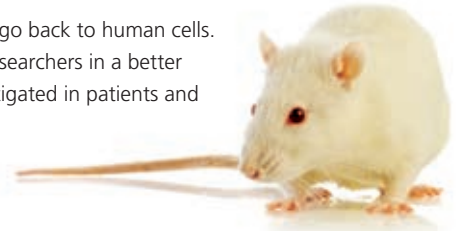


**M**ouse models have long been an invaluable tool for studying diseases. For several years CLL was a notable exception because successful mouse models for CLL were remarkably difficult to establish. Within the last seven to eight years, scientists succeeded in obtaining reproducible CLL mouse models. Several such mouse models are now available, and the previously unknown role of numerous genes in CLL is gradually coming to light.

There are various types of mouse models for CLL and various ways of reproducing CLL in a mouse model. The most popular CLL model is the transgenic mouse obtained by inserting a gene called Tcl-1 into the B-cells of the mouse. This insertion causes the mice to develop a CLL-like disease as the mice age.

Mouse models are important for CLL patients for several reasons. The transgenic mice have provided new information on genes relevant for the development of CLL. Also, genes suspected to influence the natural history of CLL can be easily tested to understand their role. Researchers can cross the transgenic mouse with another mouse in which the gene under scrutiny has been switched on or off. The offspring of these mice clarify whether the activation, or inactivation, of that specific gene increases the aggressiveness and progression of the disease.

To precisely define gene significance, researchers must go back to human cells. The knowledge gained from the mouse models puts researchers in a better position to decipher which molecules need to be investigated in patients and where to look.

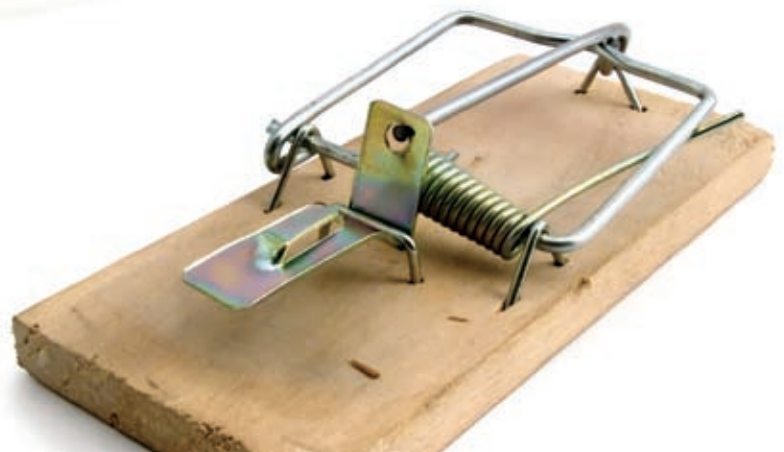


If a new molecule is proven to be important, it can become a target for new drugs. Additionally, it may be used as a marker to define a distinct subgroup of CLL patients that may benefit from specific therapeutic strategies.

Another mouse model that has proven successful is a particular xenograft model in which a human tumor is inserted into an immune-compromised mouse. Various treatments can then be tested on the mouse. The CLL in these mice closely resembles aggressive human CLL. The xenograft mice are being used to investigate the efficacy of new promising therapeutic agents and new immunotherapeutic approaches. These mice allow for conclusive results in a short period of time.



It is reasonable to foresee that improved understanding of CLL and ultimately the discovery of a cure lies in the hands of investigators able to move laterally between mice and men and between experimental and clinical research. ::



# Signal Transduction Inhibitors:

## A BRAND NEW WORLD

**D**riven by continued clinical and laboratory research, the treatment of chronic lymphocytic leukemia (CLL) has come a long way. It has evolved from single agent chemotherapy to multiagent chemotherapy, and more recently, to the combination of chemotherapy with monoclonal antibodies – so called “chemoimmunotherapy”. Patients have benefitted greatly from these advances, with improved rates of complete remission and a higher fraction of durable long term remissions.

Although these advances have been made and some battles have been won, the war against CLL continues, and challenges still remain. Chemoimmunotherapy is often limited by infusion reactions, chemotherapy toxicities, and low blood counts that are often not tolerated in older patients. Relapsed or resistant disease continues to be a clinical challenge and an important area of research.

As more is learned about the biology of CLL, it is becoming apparent that the next advances in the treatment of CLL will come in the realm of blocking signal transduction- the mechanism in which cells receive and send signals in order to function.

Several groups of CLL investigators have uncovered the importance of the B-cell receptor (BCR), which is an important protein that sits on the outside of a malignant CLL cell. Through this receptor, the CLL cell is able to receive signals from its external environment.

“the next advances in the treatment of CLL will come [from] blocking signal transduction.”

These signals are important in supporting the survival of the cancer cell, stimulating it to grow and also promoting retention of CLL cells in the tissues where they are sheltered from the effects of standard chemotherapy. Scientists have found that the signals through this receptor are communicated through a network of different proteins within the cell.

Among the proteins that make up this communication network are: Syk, Lyn, Btk, and PI3K. If one or several of these proteins could be disrupted by a targeted drug, signals through the receptor could be effectively blocked. As a result, the malignant CLL cell would not receive the appropriate signals to grow, survive and hide from chemotherapy. This could potentially lead to the release of the CLL cells from the tissues and subsequent death. This also could make them more sensitive to standard chemotherapy.

Investigation into these signaling proteins has led to the development of several drugs that target them. Drugs that target Syk, Btk, Lyn, and PI3K are currently in clinical trials in patients with CLL to study their efficacy (see table below). A major feature of these drugs is that they are given by mouth and have very few recorded side effects.

If these drugs show promising activity, future trials using them in combination with other CLL drugs such as chemotherapy or monoclonal antibodies may be planned. Such combinations can help to address the challenges of relapsed and resistant disease and perhaps further improve current remission rates. ::

SYK INHIBITOR/FOSTAMATINIB	BTK INHIBITOR/PCI-32765
<p>Oral inhibitor of the Spleen tyrosine kinase (Syk). Phase III clinical trial completed in B-cell lymphoma/CLL. Results presented at 2008 American Society of Hematology Annual Meeting demonstrated fostamatinib to be very active against CLL. Most recent research on this agent has been focused on rheumatoid arthritis (RA). A paper published in <i>The New England Journal of Medicine</i> demonstrated a very significant improvement in the outcome of RA. Thus it is very likely that this drug will come back to the CLL research environment.</p>	<p>Phase I clinical trial currently ongoing for untreated and previously treated CLL patients. The oral compound has shown significant inhibition of a key enzyme, Btk (Bruton’s tyrosine kinase), which plays a role in B-cell activation. Initial reports suggest that a majority of patients are responding to the therapy. Lymph nodes shrink dramatically within a period of weeks. B-cells are liberated and move from the lymph glands into the body’s circulation where they become more susceptible to either attack by other agents or to natural death.</p>
LYN INHIBITORS/DASATINIB & BAFETINIB	PI3K INHIBITOR/CAL-101
<p>Lyn kinase is another key enzyme in CLL cells that is responsible for cell survival. Laboratory studies show that inhibition of Lyn kinase in CLL cells results in the death of CLL cells. Drugs that have the ability to inhibit Lyn kinase should have some effect on CLL cells. Both dasatinib and bafetinib are currently being studied in CLL patients. Results from these studies will provide useful information.</p>	<p>Another important enzyme is PI3 kinase delta. This enzyme is inhibited by an agent called CAL-101 which has been demonstrated to be very active in CLL. Ongoing studies include a trial examining the combination of CAL-101 and rituximab in elderly patients with previously untreated CLL or SLL (small lymphocytic leukemia). There is also an ongoing study in conjunction with bendamustine.</p>

# CLL IN THE ELDERLY: Past, Present & Future



**C**hronic lymphocytic leukemia (CLL) is usually predominant in older individuals. The median age of patients at time of diagnosis in the United States is 72 years. In the past, physicians would reassure patients diagnosed at an older age with phrases such as “this is a good type of leukemia to have” or “this is a type of leukemia that you will die with but not one that you will die from.”

Such statements are not supported by epidemiological data. Data from the Surveillance Epidemiology and End Results (SEER) Program, which provides cancer statistics for the United States, indicates that CLL in patients age 65 or older is accompanied by an increase in mortality. Clinical trials have also shown that being older has a negative impact on treatment.

Patients over 70 years of age more often tend to be anemic and present with more advanced stage disease. Larger studies, mainly conducted by the German CLL Study Group, show that 60% of the CLL patients over 70 years of age will have at least one other comorbidity and 25% of that group will have two or more comorbidities. Comorbidities indicate other severe health conditions such as emphysema, coronary artery disease, severe diabetes, etc.

Historically, only a minority of older patients were enrolled in clinical trials. Clinical trials often have enrollment criteria which automatically excludes older patients. The results of the clinical trials then become more pertinent to those patients under 65. In the last few years there has been a significant effort to collect more information on the tolerance of treatment in older patients and on what approaches will most benefit this group.

There is an ongoing debate as to the best treatment for older patients. Traditionally, older patients have been treated with agents such as oral chlorambucil. The intent was to control the disease for as long as possible without expectation of a major impact on the disease. The approach has changed recently.

Evidence now shows that older patients in excellent general condition, with normal kidney function and without comorbidities, can benefit from a more aggressive initial therapeutic approach. These patients are often given a fludarabine based combination such as the chemoimmunotherapy combination of fludarabine, cyclophosphamide and

rituximab- FCR. This provides a benefit in terms of disease control and survival.

Presently, different approaches for older CLL patients at various fitness levels are being investigated. The new immunomodulatory agent lenalidomide is well tolerated by older patients and seems to be very beneficial based on available data. Other regimens consisting of monoclonal antibodies, immunoregulatory agents and reduced doses of chemoimmunotherapy have been evaluated in the elderly. These new agents have provided positive feedback in terms of tolerance, duration and effectiveness in controlling the disease.

Finding the right therapy for older CLL patients is a complex clinical scenario. Treatment options need to be balanced by the fitness status and related medical conditions. The best way to advance the understanding of treatments in the elderly is to encourage older patients with CLL to participate in novel studies that are specifically designed to answer questions facing this subgroup of patients. ::

## CLL GLOBAL HOSTS

# Patient Symposium

**C**LL Global Research Foundation recently sponsored an educational session for patients and donors in the Houston area. The program, held on October 12, 2010, was designed to give patients and donors an opportunity to hear presentations on the latest CLL research from some of our CLL Global grant recipients. Participants had an opportunity to engage in discussion with some of the thought leaders in CLL.

Hosted by Dr. Keating, the event afforded Drs. William Plunkett and William Wierda, both of MD Anderson Cancer Center and grant recipients of the U.S./European Alliance for the Therapy of CLL, to present their recent research. Dr. Wierda spoke about the latest findings on vaccines and immune agents while Dr. Plunkett's talk explored the popular area of targeted therapies. Dr. Keating informed the group of the latest in the area of transplant and gave details about what can be expected in the future.

There was ample opportunity following the presentations for additional discussion and for the audience to pose questions to the experts. Among the more popular questions were those dealing with whether it is advisable to get certain vaccinations, such as the flu shot, and inquiries about new treatments and how soon they will become available. The feedback from those who attended has been very positive. We received a few suggestions for additional topics that we hope to present at future sessions.



The presentations that were given at the symposium were recorded, and we plan to put these presentations on our website, [www.cllglobal.org](http://www.cllglobal.org), in the near future so all interested parties can benefit from the program. In addition, we hope to host additional educational sessions in other areas of the country where there is a concentration of CLL Global supporters. Stay tuned. ::





# Unscrambling PROGNOSTIC FACTORS IN CLL

**P**atient care is moving into the personalized era. Physicians are using prognostic factors to understand each patient's disease and the potential need and response to treatment. For proactive patients, it is important to understand these factors and how they influence their care.

Historically, the Rai and Binet staging systems have been the basis for determining the extent of a CLL patient's disease. Patients are categorized (Rai Stage 0-IV in the U.S. and Binet A-C in other countries) based on white cell count; lymph node, spleen and liver involvement; and whether the bone marrow produces normal levels of red cells and platelets. Today, treatment decisions are partially based on the stage, but other factors have come into play to better categorize CLL patients.

While the Rai and Binet staging systems include physical examination, most other prognostic factors rely on blood tests. The beta-2 microglobulin level is an important prognostic factor. This simple, easily reproducible test is very reliable in predicting the need and response to treatment and overall survival.

High beta-2 microglobulin levels indicate the CLL will progress quicker and treatment will be needed sooner than with low levels of beta-2 microglobulin. Standard levels vary from institution to institution. An individual's beta-2 level can change with disease progression. Compared to the staging systems, beta-2 microglobulin is more powerful in predicting the likelihood of patients responding to treatment and overall survival.

Cytogenetics measures abnormalities in chromosomes using a technique called FISH (fluorescent in-situ hybridization). Many CLL patients lose portions of chromosomes or gain an additional chromosome number 12. The specific chromosome abnormality provides physicians prognosis clues.

Patients with a loss of chromosome 17 (17p-) have a shorter time to disease progression and a less favorable response to treatment. However, this prognosis varies based upon disease stage and the percentage of CLL cells with the abnormality. An abnormality to chromosome 11 (11q-) indicates a patient will require therapy sooner. Generally, the response to treatment is good but with shorter remissions.

Loss of part of chromosome 13 (13q-) is associated with a longer time to disease progression, a good response to treatment and a good remission duration and survival. Patients with an additional chromosome 12 (trisomy 12) tend to need therapy but have an outstanding response to treatment. To make things more confusing, patients can have any combination of chromosomal abnormalities or no detectable abnormalities.

The mutation status of the IGVH gene has proven incredibly reliable in predicting disease progression, remission duration and overall survival after treatment.

Patients can be classified into two subgroups: mutated and unmutated. Patients with a mutated IGVH gene (approximately 60% of CLL patient) have a more favorable outcome. Unlike other prognostic factors, the IGVH mutation status does not change.

Two surface proteins, CD38 and ZAP70, appear to be correlated with IGVH mutation status. Approximately half of CLL patients have a positive CD38 or ZAP70 expression on their CLL cells. Positive expression seems to correlate with an unmutated status; one or both of these markers may potentially be used as a surrogate marker for the IGVH gene. Testing the IGVH gene is expensive and not available at all diagnostic facilities. CD38 and ZAP70 can be easily tested.

Results of CD38 and ZAP70 tests can be contradictory. The presence of CD38 indicates a more aggressive disease. However, CD38 can oscillate through the course of the disease. ZAP70 is an enzyme that should not be present in CLL cells. Positive ZAP70 expression, much like CD38, tends to be somewhat associated with a shorter time to treatment and survival rates. ZAP70 currently lacks standardization among laboratories. Patients will continue to be tested for these proteins until the impact of both ZAP70 and CD38 are fully understood.

If a patient reaches the point of needing treatment, the prognostic factors have different impacts. 17p- is the only chromosomal abnormality that has a definitive impact on patients' response to treatment and remission duration. The IGVH mutation status and ZAP70 tend not to predict whether a patient will respond to treatment, but do have an impact in predicting how long patients will stay in remission. Once a complete remission is achieved, prognostic factors other than 17p- and IGVH mutation status tend to be less important.

The most important advice for patients is to not be disturbed by any one prognostic factor. Very few patients have all favorable or all unfavorable factors. There are many patients who statistically speaking should not be doing well, but are thriving. A number of patients with 17p deletion will be observed for many years without needing therapy. Patients should never place too much emphasis on news of a positive ZAP70 or 17p deletion.

Experts can put all of these parameters in perspective. There is an abundance of new information regarding prognostic factors in CLL which still needs to be interpreted. Time and rigorous evaluations will improve the usefulness of these factors to categorize and treat patients. In the meantime, new therapies are emerging that are truly novel, powerful, user friendly and will lead to the next generation of improved outcome in patients with CLL. ::

## CORD BLOOD

# May Strike a Match

Some patients do not respond well, or at all, to current chemo or chemoimmunotherapies. These patients are considered high-risk and are in need of new treatment options. Allogeneic stem cell transplantation (receiving stem cells from a donor) is a potentially curable treatment option for patients with high-risk hematologic malignancies, including CLL. The concept is that donor cells can recognize cancer cells as foreign to the body and destroy them.

HLA-typing is used to match patients with donors by testing molecules on both of their immune cells. Having a higher number of matched molecules between donor and patient means there is a better chance for a successful transplant. Also, there is a reduced chance that the donor cells will attack the patient's body. This attack is called graft versus host disease (GVHD) and is a major concern with transplantation. It can be chronic or even fatal.

A significant proportion of patients, especially non-Caucasian patients, are unable to find a matched donor for this potentially life-saving treatment. Scientists have been searching for an alternative for these patients and are on the verge of new options.

Cord blood has emerged as an important source of stem cells for transplant patients lacking a matched donor. Since 1988, the use of cord blood transplantation has increased dramatically. There are major advantages of a cord blood transplant compared to allogeneic transplant.

Cord blood stem cells are readily available and more easily acquired than donor stem cells. Requirements for HLA matching are less stringent. There is a higher likelihood of finding a match for a minority patient, and a decreased incidence of GVHD has been noted.

Because cord blood does come from umbilical cords of infants, there is a low count of stem cells compared to the amount collected from donor stem cells. This is a major disadvantage which results in delays in the stem cells functioning in the patient (known as engraftment) and delays in immune reconstitution. These delays expose cord blood recipients to a wide array of serious and often fatal infections. This is currently the leading cause of death in these patients, but researchers are anxious to change this statistic.

Projects are being funded by CLL Global to enhance the capabilities and outcomes of cord blood transplants. Strategies that decrease the incidence of post-transplant infections while maximizing CLL specific immune responses will improve cord blood transplantation for patients (particularly minorities) who do not have other therapeutic options.

Researchers can teach cells to perform a specific function by manipulating certain molecules on cells. Drs. Catherine Bollard (Baylor College of Medicine) and Elizabeth Shpall (MD Anderson Cancer Center) are manipulating Natural Killer cells to treat CLL. Natural Killer cells, like T-cells, are immune cells that fight off infection. Because of the previously noted delays associated with cord blood transplantation, Drs. Bollard and Shpall want to expand the cord blood cells to make them more powerful. This will not only provide a targeted defense against the CLL cells, but will speed up immune recovery.

Laboratory studies are currently being conducted with the intention of initiating a clinical trial. This strategy will be used initially to improve cord blood transplantation, and in the future can potentially be used as a cellular therapy without a stem cell transplant.



Dr. Chitra Hosing (MD Anderson) is collaborating with Dr. Shpall and Dr. William Wierda (MD Anderson) to focus on relapse and infections after a cord blood transplant. They hypothesize that infusing cord blood transplant recipients with manipulated T-cells may help the body ward off infections and prevent relapse. T-cells from cord blood are manipulated to specifically target CLL cells and are enhanced so that they are more powerful. Infusing these CLL-specific T-cells derived from cord blood might boost the patient's response to the transplant and improve outcomes. Screening of patients has started for the clinical trial based on this project.

If successful, these projects will define the use of safer and more effective cord blood transplants for patients lacking appropriate bone marrow donors. Furthermore, the development of these novel therapies will provide critical tools for the treatment of CLL (and cancer in general) outside the transplant setting. ::

IN THE SPIRIT OF THE SEASON, WE ENCOURAGE  
YOU TO HONOR YOUR LOVED ONES OR YOURSELF  
WITH A GIFT TO CLL RESEARCH. FIND OUT MORE  
AT [WWW.CLLGLOBAL.ORG](http://WWW.CLLGLOBAL.ORG)

