

CLL GLOBAL HAS PROVIDED OVER 24 MILLION IN RESEARCH FUNDING (2005-2016)

## CURING CLL—THE BIG PUSH

BY MICHAEL J. KEATING, MB, BS

### CLL—A Disease Under Attack

We continue to make great strides towards finding a cure for CLL. We are now able to more accurately identify which patients are in need of therapy and which patients should delay treatment. In CLL, we are fortunate to have at our disposal a number of new potent and safe agents, new approaches to therapy, and a variety of forms of immune modulation. For the first time there is substantial evidence that a large number of patients, 1 in 3, will have a greater than 10 year failure-free survival (a continuous complete remission for greater than 10 years). However, while it is nice to see these good results, we have to remember that the hole in the donut represents patients who are not being well controlled by our present medications.

The largest group of patients for whom we have available data demonstrating outcomes are those in the so-called watch and wait category (W&W). A nomogram we developed predicts the probability of these patients needing intervention within 2-3 years. For those patients needing intervention, treatment regimens have been developed to try to achieve minimal residual disease (MRD) negativity (no detectable CLL cells in the blood or bone marrow). Previous studies in W&W patients used an ineffective chemotherapy agent, chlorambucil, with its associated DNA damage that could contribute to the development of other cancers. The current course of action includes treatment with ibrutinib and following the outcome of these ibrutinib-treated patients over time.

An additional treatment option that is in the pipeline for patients is an intriguing DNA vaccine against the enzyme telomerase. This vaccine was developed at



the Pasteur Institute in Paris. It will be offered to W&W patients who show high expression of telomerase. This study group can be identified by use of the aforementioned nomogram. The goal in treating these patients is to achieve an MRD-negative state and delay the need for therapy for more aggressive CLL.

An important element directing the treatment of CLL patients is the identification of genetic changes which occur in CLL cells. The most common abnormalities identified are deletions of portions of the chromosomes 13q, 11q, and 17p. These are extremely useful in the identification of risk. It is additionally important to note that the trisomy of chromosome 12 is no longer considered to be adverse, and that patients with this genetic abnormality respond very well to

chemoimmunotherapy programs. Other adverse genetic abnormalities have been identified by next generation sequencing (NGS), including, NOTCH1 and SF3B1. Studies are ongoing to find drugs that can target these abnormalities.

## How to Cure CLL

Currently, the goal guiding the initiation of treatment for CLL is the total clearance of the disease. The traditional complete remission (CR) criteria, however, are now considered to be inadequate. If patients achieve this so-called CR but still have residual disease identified in the blood and/or bone marrow by flow cytometry, they are likely to relapse. We can now identify one CLL cell in 10,000 normal blood cells (MRD positivity) using the cells' abnormal surface proteins. Interventions to attempt to eradicate the remaining CLL cells are underway using targeted therapies such as venetoclax, CAR T-cells, NK cells, and other forms of immunotherapy. Whereas the CLL cells formerly could be identified by four-color flow cytometry, now, however, six and eight color flow cytometry has increased the sensitivity, and thus our ability to predict when to initiate treatment with targeted therapies.

A number of groups are also developing plasma DNA measurements to identify the abnormal clones. This promises to give much more accurate measurements of the total tumor burden present after therapy.

## All Patients Need Improved Frontline Protocols

The development of new agents and improved monoclonal antibodies provides an opportunity to explore new treatments not only for patients under the age of 70, but older patients as well. Patients with a mutation in their immunoglobulin heavy chain (IgVH) are most likely to experience a cure. The fludarabine, cyclophosphamide, rituximab (FCR) chemoimmunotherapy program is most effective here, but a recently developed program of F+C together with an improved monoclonal antibody, obinutuzumab (Gayzva), plus ibrutinib has been developed. After 3 courses the majority of patients in this preliminary program have achieved MRD negativity.



Dr. Michael Keating from MD Anderson Cancer Center, Dr. Nicole Lamanna from Columbia University Medical Center, and Dr. Zeev Estrov from MD Anderson Cancer Center discuss the latest in CLL.

This is 2-4X the likelihood of achieving MRD negativity with the FCR regimen.

Patients who are unmutated, greater than 65 years of age, previously treated and relapsed are now being treated with a combination of two targeted therapies, namely ibrutinib and venetoclax. These combinations are proving to be very well tolerated with a rapid improvement in the size of lymph glands, spleen, and other sites. The promise of venetoclax to eradicate residual CLL cells from the marrow has been found to be substantiated.

Other cancers are a significant concern in CLL, namely melanoma, squamous and basal cell carcinomas of the skin, Merkel cell tumor, acute myeloid leukemia, and possible myelodysplastic syndrome in those receiving chemotherapy regimens. These targeted therapies appear to decrease the risk of developing other cancers. Identifying pre-cancerous lesions by dermatologists with appropriate initiation of treatment is important to reduce the morbidity and mortality in CLL patients.

## Tumor Dysfunction

A major problem facing CLL patients is the immune dysfunction which occurs in association with the disease or as a result of treatment for the disease. Technology is now available to remove a patient's

immune cells from the blood, expand these immune cells in the lab, and then return the cells to the patient. In addition, some agents such as lenalidomide (Revlimid), have the ability to increase the T cell lymphocyte number and function in vivo. This immune restoration helps to eradicate CLL cells, which in turn helps patients develop a fully functional immune system with a decreased incidence of other cancers.

Curing CLL is no longer a pipe dream. The time is right for us to push for greater efforts towards this end. While eradication of CLL and prolonging life is crucial, the ability to have patients maintain full functionality with no increased risk of developing second cancers is a complementary goal for patients, physicians, and their teams.

*(While all of us appreciate gifts, especially this time of year, many whom we serve hope and pray only for the gift of life itself. I speak for all the CLL physicians, scientists, nurses, and staff in saying that it is our honor to serve as allies with our patients in their search to achieve this most valuable of gifts. Please join us and our patients in this effort as you contribute to organizations that support the achievement of the precious gift of life – the finest gift of all.)*

Yours truly,



## **LIVING WELL WITH CLL— NEW YORK, NEW YORK**

In addition to our commitment to fund cutting-edge research, CLL Global is committed to bringing the most up-to-date information to our patients. In this regard, CLL Global, in conjunction with our production partners at Patient Power, the Patient Empowerment Network, and Columbia University Medical Center, held a Town Meeting at The Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center in New York, NY, on May 14, 2016. Speakers at the meeting included Phillip Thompson, MB, BS from MD Anderson Cancer Center, Esther Schorr, the online host as well as a caregiver and patient advocate, Andrew Schorr, event host and a two-time cancer survivor and patient advocate, Tina Sapienza, LMSW, OSW-C from Columbia University Medical Center, Jennifer Abraham, a patient advocate, Nicole Lamanna, MD from Columbia University Medical Center, Christine Bladwin, MSN, RN, NP-C from Columbia University Medical Center, and Larry Kaagen, a patient advocate (left to right in photo below). Topics addressed at the meeting included what it means to achieve MRD-negative status, personalized care and CLL, discussion of the differences between CLL and SLL, and how CLL inhibitor treatments work. Information and videos from the event can be found at <https://www.patientpower.info/event/cll-nyc-2016/>. We will co-host two town meetings in 2017 in Houston, TX, and Portland, OR. Free registration to attend these events in-person or online will be available soon on the Patient Power website ([www.patientpower.info](http://www.patientpower.info)).



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## SPECIAL THANKS TO OUR PATRONS

Philanthropic support is a wonderful way to honor or memorialize someone, and CLL Global often receives donations from friends and family members for this purpose. In 2016 we were fortunate to be the recipient of one such donation from the Eyad Karkoutly Foundation.

On Saturday, April 9, 2016, Dr. Ayman and Mrs. Susan Karkoutly, founders of the Eyad Karkoutly Foundation, hosted a fundraising event to support CLL Global Research Foundation. The event featured live music by David Brandon as well as a presentation by guest speaker,

CLL Global President and CEO Dr. Michael Keating. The event raised \$20,000 to support CLL Global-sponsored research.

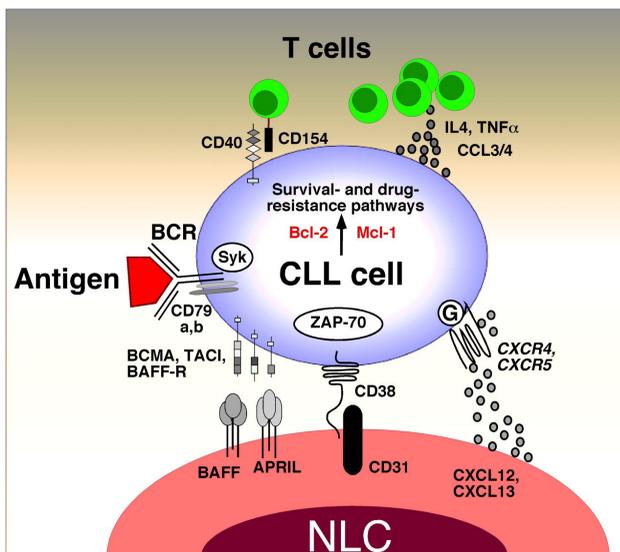
The Eyad Karkoutly Foundation was founded in honor of Eyad Karkoutly who was diagnosed with CLL and succumbed to the disease in 2014. The mission of the foundation is to monetarily support the research of blood cancers in an effort to advance treatment options for CLL patients. CLL Global is honored to have been the recipient of this donation, which is being used to support our newly-established Alliance working groups, described below.

## ALLIANCE MICROENVIRONMENT WORKING GROUP

CLL Global formed our Alliance research collaborations to bring together leading CLL scientists and clinicians from around the world in a collaborative and open environment. This innovative approach to research overcomes many of the obstacles presented when research is performed in silos, as it so often is. We typically hold two scientific conferences per year, one in the United States and one outside the States, giving our members the opportunity to present their latest findings and brainstorm future research endeavors. Over the last 10 years these collaborations have been incredibly fruitful, producing over 150 peer-reviewed publications, multiple patents, and adding to the evidence that has led to many new treatment options for CLL patients, including ibrutinib, idelalisib, and venetoclax.

We have recently initiated a new round of Alliance projects with a thematic approach. Themes for these working groups include the CLL microenvironment, CLL genetics, drug development, immune deficiency, and immunotherapy. Three to five experts in each area will be recruited and invited to submit a research proposal. Upon successful peer-review of the proposal, CLL Global will commit \$1.5 million over three years to the project. By removing obstacles and providing committed funding to each group, we will greatly accelerate advances in the treatment and cure of CLL.

At this time we have finalized assembly of the Microenvironment working group, the proposal has been peer-reviewed, and the funding allocated. Keep reading below to meet the team of scientists and learn about how your donations are being used to ensure, in the words of our President and CEO Dr. Michael Keating, that “the best is yet to come”.



### Cross-talk between CLL cells and the lymph node microenvironment

This figure displays the molecules involved in cross-talk between CLL cells and accessory cells in the lymphoid tissue microenvironments. Contact between CLL cells and nurselike cells (NLCs) is established and maintained by chemokine receptors and adhesion molecules (CXCL12, CXCL13, CXCR4, CXCR5). This cross-talk between CLL cells and accessory cells results in activation of survival and drug resistance pathways, such as those provided by Bcl-2 and Mcl-1.

Burger and Gandhi, Blood. 2009. 114:2560-2561



Dr. Nicholas Chiorazzi is an investigator and head of the Karches Center for Chronic Lymphocytic Leukemia Research at The Feinstein Institute for Medical Research located in Manhasset, New York. His research focuses on investigating the activation and maturation of B-lymphocytes in health

and disease, particularly in CLL. Dr. Chiorazzi has been an active collaborator with CLL Global Research Foundation since its inception, and is currently the lead for our newly-established Alliance microenvironment working group.

### **Abstract—Chiorazzi**

The leukemic cells from patients with CLL cannot survive and grow in people by themselves. They require survival cues from other cells in the areas where they live. These areas are called the “tissue microenvironment”.

There are several types of cells that live in the tissue microenvironment and among these are T lymphocytes of different kinds (T-cell subsets) and myeloid-derived suppressor cells (MDSCs). Based on the kind involved (Th1 cells, Th2 cells, Th17, cells, and others), the former cells can provide EITHER survival and growth inputs OR death signals. Therefore, being able to determine the kind of cell that is dominant in an individual patient is critical for clinical course and outcome. Likewise and again based on the kind involved (granulocyte-like MDSCs and monocyte-like MDSCs), the latter cells can also provide EITHER survival and growth inputs OR death signals. Finally, these two kinds of cells (specific T-cell subsets and specific MDSCs) communicate with each other, and this communication alters the balance between survival/growth signals and death signals that each imparts.

In years 1 and 2, each section will develop an understanding of the interactions of the various players in this 3-way dialogue, and then in year 3 will use this information to develop new treatments.

Finally, the studies in these sections are linked in multiple ways to experiments being carried out by the 4 other members of this investigative team: Drs. Sabrina Bertillacio, Jan Burger, Zeev Estrov, and Katy Rezvani.

### **Abstract—Bertilaccio**

CLL is the most frequent adult leukemia in the western world and results from the accumulation of mature neoplastic B lymphocytes. Despite the use of intensive immune-chemotherapeutic treatments, CLL is still an incurable disease. Given that extensive studies demonstrate how leukemic development and expansion correlate with microenvironmental stimuli delivered by non-malignant cells, a way to modify the present therapeutic perspective could derive from a better understanding of the biological mechanisms underlying the microenvironment-based molecular and cellular interactions. The role of the monocyte/macrophage lineage in leukemic progression and dissemination is poorly understood. Still therapeutic approaches aimed at targeting the monocyte/macrophage-CLL cell interaction are unexplored. The integration of different approaches shuttling between human primary cells and animal models have already led to solid preliminary data and will allow the analysis of the molecular mechanisms that regulate cellular cross talk between leukemic and monocyte/macrophage lineage cells. Overall these approaches will lead: a) to understanding the functional, cellular, and molecular dynamics of leukemic cell-monocyte/macrophage interactions that occur in CLL, and b) to explore and validate novel therapeutic approaches aimed at targeting the monocyte/macrophage lineage.



**Dr. Maria Theresa Sabrina Bertilaccio** is a senior research scientist in the Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Center (MDACC). She was recently recruited to MDACC from the Unit of Lymphoid Malignancies, San Raffaele Scientific Institute in Milan Italy. Her research focuses on the role of crosstalk between monocytes, macrophages, and leukemic cells in CLL progression



**Dr. Jan Burger** is an Associate Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston Texas. Dr. Burger's interests are in the treatment of patients with acute and chronic leukemias and myelodysplastic syndromes, in addition to his research interests in the development of pre-clinical and clinical models to target the microenvironment in acute and chronic leukemias.

### **Abstract—Burger**

Activation of the B cell receptor (BCR) is one of the most important events in CLL development, and is successfully de-activated by the kinase inhibitors ibrutinib and idelalisib, which target BCR signaling. To understand the mechanism that activates BCR signaling in CLL, we propose to utilize a model system called “nurselike cells” (NLC) which are feeder cells that keep CLL cells alive and activate the BCR. We propose to identify which molecules on the surface of NLC activate BCR by tagging them with purified BCR from CLL patients and then identifying the BCR-recognized proteins by a method called mass spectrometry. Using this approach, we hope to identify and then validate molecules that trigger BCR activation which could lead to new and more targeted therapy approaches. In our preliminary studies we already have identified potential targets of interest, but validation and repeat experiments will be necessary and will be conducted under this proposal. Overall this research will give insight into leukemic disease mechanisms, the BCR, and its mode of activation, which are central to the disease biology and therefore likely will give us a better understanding, potentially leading to the discovery of new therapeutic targets.

**Dr. Zeev Estrov** is a Professor of Medicine and Internist in the Department of Leukemia at The University of Texas M.D. Anderson Cancer Center. Dr. Estrov's research focuses on the biology of normal and leukemic hematopoietic stem cells.

### **Abstract—Estrov**

Chronic Lymphocytic Leukemia (CLL) patients who have a high monocyte count have a poor prognosis and an increased frequency of CD14+ HLA-DR lo/neg monocytes is associated with decreased time to progression. In in vitro studies monocytes increase the survival of CLL cells. Further, in vitro studies demonstrate that monocyte-derived nurse like cells provide CLL cells with a survival advantage, suggesting that CLL patients' monocytes support the CLL clone. We and others found that monocytes isolated from patients with CLL are different from those isolated from healthy individuals. CLL-derived monocytes are characterized by an altered composition and dysregulation of genes involved in phagocytosis and inflammation, suggesting that leukemia-mediated “education” of immune cellular elements may also include the establishment of a skewed phenotype in the monocyte/macrophage population in patients with CLL.

The goal of this project is to determine how monocytes support CLL cells and identify the means of inhibiting this effect. We intend to determine how CLL cell-derived RNA strands and CLL cell-derived exosomes “educate” healthy donor monocytes, and compare their modified gene expression profile to that of CLL-derived monocytes. We will isolate, expand, and study the characteristics of CLL-derived fibrocytes. Fibrocytes are CD14-derived cells that participate in the induction of tissue and bone marrow fibrosis. By using co-cultures and clonogenic assays we will investigate the effects of CLL-derived fibrocytes on CLL and hematopoietic progenitor cell proliferation and determine whether fibrocytes play a role in CLL bone marrow failure. We will also investigate whether serum amyloid P, known to inhibit the differentiation of monocytes into fibrocytes and currently investigated clinical trials, reverses bone marrow failure.





**Dr. Katy Rezvani** is a Professor in the Department of Stem Cell Transplantation, Director of Translational Research, and Associate Medical Director of the GMP laboratory at The University of Texas MD Anderson Cancer Center. Dr. Rezvani's research focuses on developing novel targeted therapies for CLL using cord blood-derived natural killer cells.

#### **Abstract—Rezvani**

Recent data support an important role for the immune system in the control of cancer. However, defects of the immune system have been described in CLL. Indeed, progressive dysfunction of the immune system often parallels disease progression.

The aim of our study was to determine the role of the innate immune system, specifically powerful immune system cells called natural killer (NK) cells, in the control of CLL. We have shown that CLL B cells can suppress T cells in the tumor microenvironment. The aim of this proposal is to understand the underlying mechanisms for this effect. A detailed understanding of the underlying mechanism for the defects in T cell function will help us develop strategies to enhance T cell function for the treatment of patients with CLL.

**CLL GLOBAL HAS FUNDED OVER  
77 INDIVIDUAL INVESTIGATORS,  
IN OVER 15 COUNTRIES  
THROUGHOUT THE WORLD.**

## **2016 YEAR IN REVIEW**

**2016 brought many new, exciting treatment options for patients with CLL. Below a few of these advances are highlighted.**

The U.S. Food and Drug Administration approved venetoclax for the treatment of patients with CLL who have del(17p) and have received at least one prior therapy. Venetoclax is the first FDA-approved treatment that targets the B-cell lymphoma 2 (BCL-2) protein, which supports cancer cell growth and is often overexpressed in patients with CLL. “For certain patients with CLL who have not had favorable outcomes with other therapies, venetoclax may provide a new option for their specific condition” said Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research.

A multi-center, single-arm trial of ibrutinib in patients with relapsed/refractory CLL with del(17p) showed an overall response rate of 83% and estimated rates of progression-free and overall survival at 2 years of 63% and 75%, respectively. The results support use of single agent ibrutinib as the initial therapy for most patients with CLL harboring del(17p) or a TP53 mutation. (O’Brien et al. *Lancet Oncology*. 2016. Oct;17(10): 1409-1418.)

#### **Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study**

Susan O’Brien, Jeffrey A Jones, Steven E Coutre, Anthony R Mato, Peter Hillmen, Constantine Tam, Anders Österborg, Tanya Siddiqi, Michael J Thimman, Richard R Farman, Osman Ilhan, Michael J Keating, Timothy G Call, Jennifer R Brown, Michelle Stevens-Brogan, Yunfeng Li, Fang Clow, Danielle F James, Abinva D Cho, Michael Hallek, Stephan Stilgenbauer

#### **Summary**

**Background** The TP53 gene, encoding tumour suppressor protein p53, is located on the short arm of chromosome 17 (17p). Patients with 17p deletion (del17p) chronic lymphocytic leukaemia have poor responses and survival after chemotherapy. We assessed the activity and safety of ibrutinib, an oral covalent inhibitor of Bruton's tyrosine kinase, in relapsed or refractory patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma.



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In a multicenter, open label trial, 564 adults with previously untreated CLL without del(17p) and without significant comorbidities were randomly assigned to treatment with fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR). Previous trials have suggested BR is slightly less effective but better tolerated than FCR. In the current

trial FCR improved median progression-free survival by 13 months. FCR remains the preferred treatment regime for younger adults with previously untreated CLL without del(17p).  
(Eichhorst et al. 2016. Lancet Oncol. 17(7):928.)

The second generation BTK inhibitor acalabrutinib was recently shown to be both safe and effective. In a trial led by Dr. John C. Byrd of The Ohio State University, 95% of patients had a complete or partial tumor response, including high risk patients with deletion 17p. Acalabrutinib is a more selective BTK inhibitor as compared to ibrutinib, providing patients with another treatment option.  
Byrd et al. 2016. NEJM 374:323-32.



### First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial

Barbara Eichhorst, Anna-Maria Fink, Jasmin Bahls, Raymonde Busch, Gabor Kovacs, Christian Maurer, Elisabeth Lange, Hubert Köppler, Michael Kahl, Martin Salkler, Rudolf Schlag, Ursula Vohring-Kaiser, Georg Köchling, Christoph Pflüger, Michael Gregor, Torben Plesner, Marek Trnicky, Kirsten Fischer, Hamut Döhner, Michael Kobza, Clemens-Martin Wendtner, Wolfgang Klapper, Karl-Anton Kreuzer, Stephan Stiglmayr, Sebastian Böttcher, Michael Hallek, on behalf of an international group of investigators and the German CLL Study Group (GCLLSG)

Lancet Oncol 2016; 17: 928-42  
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[http://dx.doi.org/10.1016/S1473-3099\(16\)00515-1](http://dx.doi.org/10.1016/S1473-3099(16)00515-1)

#### Summary

**Background** Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab is the standard therapy for physically fit patients with advanced chronic lymphocytic leukaemia. This international phase 3 study compared the efficacy and tolerance of the standard therapy with a potentially less toxic combination consisting of bendamustine and rituximab.

The NEW ENGLAND JOURNAL of MEDICINE

#### ORIGINAL ARTICLE

### Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Bonnie Harrington, D.V.M., Susan O'Brien, M.D., Jeffrey A. Jones, M.D., M.P.H., Anna Schuh, M.D., Ph.D., Steve Devereux, M.D., Jorge Chaves, M.D., William G. Wierda, M.D., Ph.D., Farrukh T. Awan, M.D., Jennifer R. Brown, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Deborah M. Stephens, D.O., Paolo Ghia, M.D., Jacqueline C. Barrientos, M.D., John M. Pagel, M.D., Ph.D., Jennifer Woyach, M.D., Dave Johnson, B.S., Jane Huang, M.D., Xiaolin Wang, Sc.D., Allard Kaptein, Ph.D., Brian J. Lannutti, Ph.D., Todd Covey, B.A., Maria Fardis, Ph.D., Jesse McCreivy, M.D., Ahmed Hamdy, M.B., B.Ch., Wayne Rothbaum, M.A., Raquel Izumi, Ph.D., Thomas G. Diacovo, M.D., Amy J. Johnson, Ph.D., and Richard R. Furman, M.D.

# THANKS TO YOUR GENEROSITY!

Over the last decade CLL Global Research Foundation has provided over \$24 million in funds to support cutting edge research on the diagnosis, treatment, and prevention of CLL. We have funded over 77 individual investigators, both new and established, in over 15 countries throughout the world. This investment has resulted in 229 peer-reviewed publications that have been cited over 8,000 times. This publication success translates into investigators receiving funding from other agencies, including the National Institutes of Health and the National Cancer Institute, which means your donation is parlayed several-fold into additional research dollars. The culmination of these investments has been the approval of many new treatment options for CLL patients, with many more in the pipeline, as well as improved diagnostics and prevention platforms. By working together to think outside the box regarding how best to address the pressing questions in CLL biology, pathophysiology, diagnosis, treatment, and prevention, CLL Global and you, our friends and patrons, are making momentous strides towards curing CLL.

## HAPPY NEW YEAR

As we move into 2017 CLL Global would like to wish everyone a joyous holiday season and a safe, prosperous and productive New Year. Please accept our profound gratitude for your continued support which makes so much possible. For our part, we very much look forward to keeping you apprised of the exciting research and best practice advances that are anticipated in the year to come.

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