

CLL GLOBAL HAS PROVIDED OVER \$27 MILLION IN RESEARCH FUNDING (2005-2019)

GREETINGS!

CLL Global is thrilled to have this opportunity to wish everyone a joyful holiday season, and to let you know what we have been up to throughout the year. As you may know, this has been a challenging time for the Foundation, but thanks to the incredible support we've received from our board of directors, scientific advisors, and you, our patrons, it has been a very successful one. We funded over \$2M in clinical and translational research projects across three continents, and we are in the process of sponsoring several international fellows, ensuring the next generation of CLL experts have the best possible training opportunities. We hope you enjoy reading about our progress, but first we'll start with a word from our founder and friend, Dr. Michael Keating:



Pictured: Dr. Michael Keating and Dr. William Wierda

GOOD DAY. IN FACT, IT IS AN EXCELLENT DAY.

I want to start by thanking everyone who has reached out to wish me a speedy recovery from my illness. Your thoughts, prayers, and kind words have been a source of joy and hope for me during my difficult recovery. It is not easy for the doctor to become the patient!

As you may know, last year I suffered a small stroke following spinal fusion surgery. As a result of the stroke, I experienced some vision loss in my left eye. Regrettably, a few months later I suffered a second, larger stroke which further affected my vision. Fortunate for me, Houston has excellent inpatient and outpatient stroke and recovery programs, and I was able to benefit tremendously from them.

I went through several months of physical and cognitive therapy, and thanks to my incredible team of caregivers who helped me to anticipate challenges and prepare for a return to work, I am now able to come into my office at MD Anderson part-time and focus on my research. I walk with a walker or walking stick, and I am continuing with my visual rehabilitation, which will hopefully improve my range of vision on the left side. Fortunately, my speech was not affected and I am working to embrace my new normal.

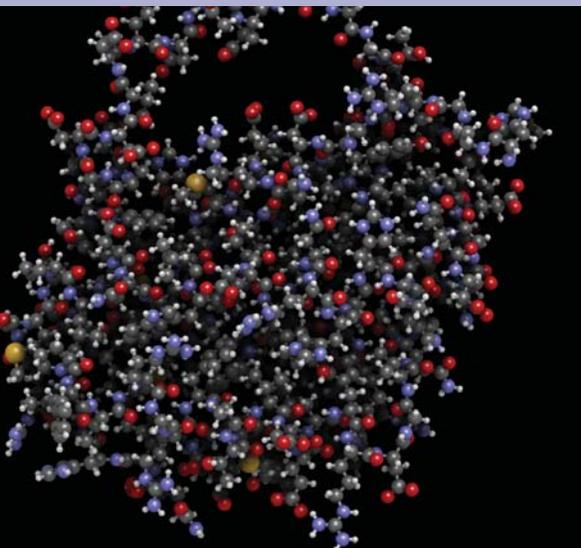
This experience has helped me fully appreciate what my patients go through in terms of accepting an uncertainty of outcome, fear of the unknown, and the difficulty of handing over control. My sincere hope is that I and the amazing team of caregivers at MD Anderson have made, and continue to make, facing a CLL diagnosis less frightening.

I am proud of the way the CLL Team performed in my absence to ensure no interruptions in patient care. While I will deeply miss seeing you all in clinic, I leave you in excellent hands. I plan to continue with my research activities, so there is no fear of my losing touch with the CLL community. I feel certain you will see my face and name pop up again in the near future. Thank you all for allowing me the honor of serving as your physician, and for accepting me as your friend. --MJK

MAKING EVERY DOLLAR COUNT

CLL Global works hard to ensure we are good stewards of the funds we receive from our donors. With regard to research funding, this means soliciting grant applications which are then reviewed by external CLL experts. Those projects that are considered promising by the external reviewers are then evaluated internally by the CLL Global Scientific Advisory Board. After these two review steps, projects that are ranked the highest are presented to our board of directors for a final approval for funding.

We are particularly excited about one project chosen to receive funding in 2019, led by Dr. William Plunkett examining which molecular characteristics of CLL cells allow them to outlive normal B cells, and how this may be exploited to develop new strategies to target and kill these persistent malignant cells. We asked Dr. Plunkett to explain the strategy behind the project.



The Bcl-2 (B-cell lymphoma 2) protein family are a group of proteins that regulate cell death (apoptosis) by either blocking (anti-apoptotic) or inducing (pro-apoptotic) apoptosis. Damage to the Bcl-2 gene has been identified as a cause of numerous cancers including CLL, lung, breast, prostate, and melanoma.

Strategies to Understand and Target Bcl-2 Family Proteins in CLL

“Important characteristics of CLL cells are that they lack the ability to conduct the immune surveillance function of their normal counterparts, and they are able to outlive their normal counterparts. The viability of CLL cells is governed by a family of structurally-related proteins called the Bcl-2 family proteins. A major means that the Bcl-2 survival proteins use to extend the life of the CLL is by binding to and inhibiting other Bcl-2 family proteins that normally initiate the process of cell death. Thus, the balance between pro-life and pro-death proteins determine whether the CLL cell will live or die. This has been the basis for the development of therapies, a few of which are now in the clinic. A missing portion of our understanding of how this balance is regulated is knowledge of how many of each of these proteins the CLL cell contains, and how this affects different responses to therapies. We are proposing to use a new method that quantifies the amount of pro-life and pro-death Bcl-2 proteins in CLL cells to answer these questions. The results of these investigations will be used to guide the design of clinical trials.”

--Bill Plunkett, Ph.D.

The Future of Cellular Therapy in CLL

This fall, MD Anderson Cancer Center and Takeda Pharmaceutical Company Limited announced an exclusive license agreement and research agreement to further develop umbilical cord blood-derived CAR-directed natural killer (NK)-cell therapies. Katy Rezvani, M.D., Ph.D. and her team developed the CAR NK-cell therapy in an effort to improve upon existing CAR treatments for CLL, as well as other hematologic and solid malignancies. Unlike CAR T-cell therapy, which takes weeks to develop and must be administered in an inpatient setting due to the potential for severe adverse reactions, CAR NK-cell therapy is readily available and in ongoing clinical trials has shown no signs of adverse events. According to Dr. Rezvani, the team’s “vision is to improve upon existing treatments by developing armored CAR NKs that could be administered off-the-shelf in an outpatient setting – enabling more patients to be treated effectively, quickly and with minimal toxicities.” Through grants provided by CLL Global, among others, Dr. Rezvani developed the CAR NK-cell therapy and initiated the first clinical trial using the therapy in CLL. From funding basic research to better understand the biology of CLL, to creating novel therapies to treat the disease, CLL Global is committed to our mission of finding a cure.

Training the Next Generation of CLL Experts

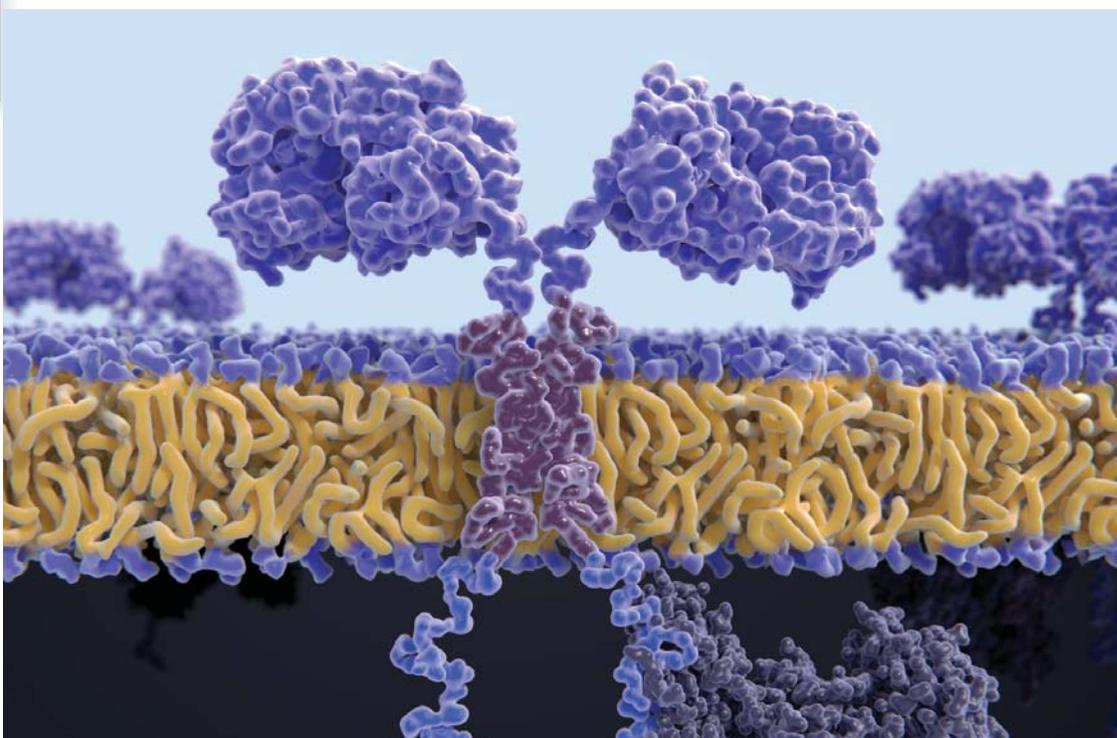
Another initiative we are excited to put into play this year is training scholarships for clinical and research fellows from around the world. Funding from CLL Global allows the fellows to travel and train with leading CLL experts, ensuring expertise in the disease continues to have a global reach for years to come. The first fellow to be recruited is Dr. Natalia Timofeeva from St. Petersburg, Russia. Dr. Timofeeva will be training with Marina Konopleva, M.D. and Varsha Gandhi, Ph.D. in the departments of Leukemia and Experimental Therapeutics at MD Anderson Cancer Center. While at MD Anderson, Dr. Timofeeva will study the abnormal metabolism of CLL cells. Keep reading to learn more about her exciting project.



Pictured: Dr. Natalia Timofeeva

Targeting Metabolic Rewiring in CLL

“Chronic lymphocytic leukemia (CLL) is a B-cell disease where patients show relentless accumulation of leukemic B-lymphocytes in bone marrow, blood, and lymph nodes. Unlike normal lymphocytes that have an 8-10 day life span, CLL cells survive for a long time in the human body. Accumulation of these cells is because of B-cell receptor pathway signaling, and survival of these cells is due to specific proteins such as Bcl-2 pro-life protein. Targeting these pro-life pathways in patients has resulted in dramatic response rates with high overall survival. Unfortunately, resistance to these agents has already been reported. Published literature and our preliminary data suggest that metabolic rewiring occurs after the development of resistance. We plan to exploit the metabolic nexus of CLL cells. For this we will test agents that target different aspects of metabolism in CLL including small molecule inhibitors of glutaminase and oxidative phosphorylation in CLL cells. We feel this unexplored territory will provide us an understanding of new pathways, changes that occur during the development of resistance, and identify new opportunities to target the resistance pathway.” --Natalia Timofeeva, M.D.



CAR NK-Cell Therapy

Chimeric antigen receptors (CARs) are a special type of receptor protein created in a laboratory. CARs are designed to bind to certain proteins located on cancer cells. In the case of CAR NK cell therapy, the CAR is added to NK immune cells harvested from umbilical cord blood, helping them find and kill cancer cells that express the specific protein the CAR is designed to bind. Once the CAR-NK is created in the laboratory, it can be infused into patients to fight their disease.

FLYING HIGH

The third annual “Fly for a Cure” fundraising event, hosted by Eyad Karkoutly Lymphoma Leukemia Research Foundation (Eyad Karkoutly Foundation), was held at the Spirit Ranch in Lubbock, Texas, on Sunday, April 28, 2019. This family-friendly event included kite flying activities, local food trucks, live music, and the chance to raise money to help blood cancer research take flight.



This year's event was the largest yet and raised \$25,000 to support CLL Global.

We are fortunate to have creative benefactors like Eyad Karkoutly Foundation President Susan Karkoutly, whose tireless efforts in memory of her son, Eyad, help ensure our ability to fund the best and brightest CLL researchers and clinicians.

Next year's event will be held on March 29, 2020. Always creative, for the fourth annual festival Susan has reached out to local schools and invited students to design and build their own kites to fly at the event. We encourage anyone living in the area to check out this colorful, fun-filled event.



CONGRATULATIONS, DR. FREIREICH, A TRUE PIONEER!



The American Association for Cancer Research (AACR) awarded cancer pioneer Emil J. Freireich, MD, FAACR, with the 2019 AACR Award for Lifetime Achievement in Cancer Research. Dr. Freireich, a CLL Global scientific advisor and board member since the Foundation's inception, and a retired professor in the Leukemia Department at MD Anderson Cancer Center, was honored for his work in establishing combination chemotherapy to treat childhood acute lymphoblastic leukemia.

“His innovations in combining therapies and finding new ways to avoid relapse changed the course of clinical research and saved the lives of entire generations of children”, said AACR chief executive, Margaret Foti, PhD, MD.

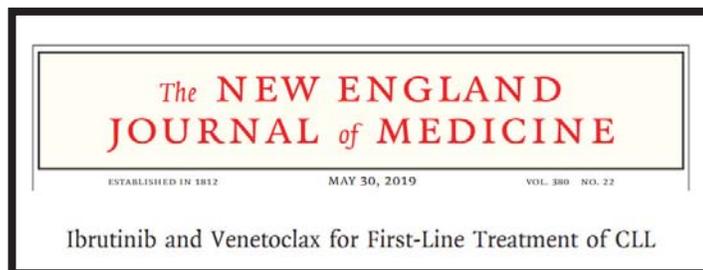
Thanks to Dr. Freireich's pioneering research, today survival rates for childhood leukemia exceed 90 percent. Please join us in congratulating Dr. Freireich on this well-deserved award.

Pictured: Dr. Emil Freireich and Dr. Michael Keating

TREATMENT NEWS

Ibrutinib and Venetoclax for First-Line Treatment of CLL

Results from an investigator-initiated phase 2 study of combination ibrutinib and venetoclax in previously untreated high-risk and older CLL patients showed the combination to be a highly effective oral regimen for this difficult to treat population. Impressively, after 12 cycles of treatment, all patients responded - 88% of patients had a complete remission and 61% had remission with undetectable minimal residual disease (MRD). This study is continuing for an additional 12 months. At the end of 12 months, those patients with undetectable MRD will cease treatment while those with detectable MRD will continue on single agent ibrutinib. Undetectable MRD can predict progression-free and overall survival, so extended follow-up of this study will provide important information into targeted therapy of CLL. CLL Global is proud to have been one of the sponsors of this exciting research study. (N Engl J Med 2019;380:2169-2171)



“Here, assessment of minimal residual disease (MRD) has replaced the progression-free survival curve of old, indicating a possible shift in focus away from traditional clinical-trial end points and toward even more stringent measures of clinical efficacy that may be central to regulatory decisions.” – A. Wiestner, M.D., Ph.D. (N Engl J Med 2019; 380:2169-2171)

Also of Note

- This year, the Food and Drug Administration (FDA) approved the combination of ibrutinib plus obinutuzumab to treat adults with previously untreated CLL. The approval was supported by results of the phase 3 iLLUMINATE trial which compared newly diagnosed CLL patients who received ibrutinib plus obinutuzumab or chlorambucil plus obinutuzumab. The overall response rate was 88% for the ibrutinib arm compared to 73% in the chlorambucil arm. (ClinicalTrials.gov NCT02264574)
- Also approved by the FDA in 2019, the combination of venetoclax plus obinutuzumab for patients with previously untreated CLL, providing a chemotherapy-free, fixed duration treatment. The approval was based on results from the CLL14 trial which showed the venetoclax-obinutuzumab combination reduced the risk of disease progression or death by 67% compared with a combination of chlorambucil and obinutuzumab. (N Engl J Med 2019;380:2225-2236)
- Results from the phase 3 E1912 trial, which compared the combination of ibrutinib plus rituximab (I-R) to the chemoimmunotherapy regime of fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated CLL patients, favored the I-R regimen. At 33.6 months of follow up, progression-free survival in the I-R group was 89.4% as compared to 72.9% in the FCR group. The I-R regime was superior to FCR in this patient population. (N Engl J Med 2019: 381:432-443)

KEEPING YOU INFORMED

CLL Global is committed to keeping patients, families, and caregivers informed on the ever-changing CLL treatment landscape. In partnership with Patient Power – A Cancer Community, CLL Global sponsors in-person and virtual patient town halls annually, providing attendees with an opportunity to learn from CLL experts, and to ask questions of those experts in real time. We also fund enduring material including expert interviews reviewing conference coverage of promising CLL treatment research, ongoing clinical trials, and newly FDA-approved treatment regimens. Find the latest information on our website, cllglobal.org, and at Patient Power, patientpower.info/chronic-lymphocytic-leukemia.



CLL GLOBAL RESEARCH FOUNDATION: FROM DREAM TO REALITY

It has been a reflective year for CLL Global and as such, we wanted to recognize the incredible impact Dr. Keating and the Foundation have had on the field of CLL. Along these lines, we reached out to one of Dr. Keating's long time collaborators, Dr. William Plunkett, Professor in the Department of Experimental Therapeutic at MD Anderson Cancer Center. Dr. Plunkett currently serves on the Foundation's Scientific Advisory Board and on the Board of Directors.

In the more than 30 years we have collaborated, I have never known Dr. Keating to be without novel ideas for advancing projects on the development of new therapeutics and treatments of CLL. This outflow of creativity and imagination has occurred virtually on a daily basis. His ideas include approaches to advance new agents, pharmacologic strategies for improving drug efficiency, considerations of mechanisms of action and identifying new targets for therapy. His ultimate goal has always been optimizing the design and evaluation of novel treatments in the clinic. This continuous flow of insight, driven by his brimming enthusiasm, started with his finding that a new agent, fludarabine, was much more effective at inducing remissions in CLL than existing treatments. His exhilaration with this success propelled him to swiftly produce a fountain of clinical results that the traditionalists could no longer refute.

Currently, it is widely accepted that it was Dr. Keating's initial findings and his compelling presentations that energized and inspired the research and clinical communities that now generate more than 1,000 publications focused on CLL each year.



Pictured: Dr. Michael Keating and Dr. William Plunkett

These initial successes with treatment of a disease that previously was without an effective therapy were greeted by patients with gratitude that was often expressed by donations intended to support Dr. Keating's research. Ironically, he perceived this as a problem because as a clinical investigator, he had no ready need for the equipment and supplies that would be well received by a research laboratory. In expressing his frustration to his mentor, Dr. Emil J Freireich, the suggestion arose of "Why don't you start a charitable foundation?" It was clear to Dr. Keating that this turned a vexing problem into a challenge that could create a greater workforce dedicated to the cure of CLL. The thought that funds provided by grateful patients and their families could advance the development of new treatments for CLL was the beginning of the CLL Global Research Foundation (CLL GRF) in 2003.

WANT TO KEEP UP WITH CLL GLOBAL ALL YEAR LONG?

SIGN UP TO RECEIVE OUR QUARTERLY NEWSLETTER ON OUR WEBSITE: CLLGLOBAL.ORG



FOLLOW US ON FACEBOOK TO GET THE LATEST NEWS ABOUT CLL, FROM NEWLY FDA-APPROVED THERAPIES, TO ONGOING CLINICAL TRIALS, AND CANCER PREVENTION RECOMMENDATIONS. : FACEBOOK.COM/CLLGLOBAL



Seemingly undaunted and certainly energized by the challenge of creating something that was completely out of his experience, Dr. Keating applied his resourcefulness, entrepreneurial nature and advice from friends to bring a not-for-profit foundation into legal status.

Pictured left to right: CLL Global Board Members Louis Katopodis, Diane Lee Kraitman, Dr. Martin Raber, Phyllis Cohen, Dr. Michael Keating, Robert Nichols, and Dr. Emil Freireich along with CLL Global Chief Development Officer Sam Pace.

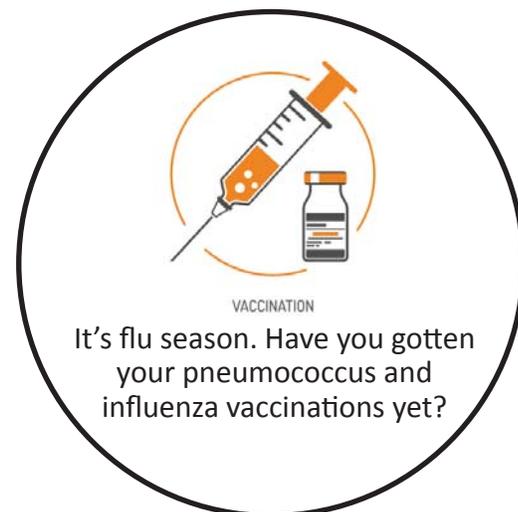
His vision at this point was to use donated funds to award 2-year grants to support the research of junior investigators with a pedigree in CLL research. This was overseen by an advisory board composed mainly of senior business leaders who had a personal commitment to CLL, a scientific advisory board made up of leaders in CLL research and treatment and one paid staff member with a background in business. Funded investigators soon brought the CLL GRF national and international recognition by citations in publications and presentations. Dr. Keating informed the CLL patient community directly with his periodic newsletters to spread the news of the CLL GRF.

Within five years, donations had reached a level that allowed Dr. Keating to create the US-European Alliance for CLL to fund leading CLL research laboratories internationally as well as nationally with the intention of increasing the breadth of areas from which new therapeutic approaches could be generated.

With hindsight, it is clear that Dr. Keating's vision and efforts with CLL GRF provided an understanding of the biological basis for the disease and generated the stimulus for the development of major areas of current CLL therapies including chemoimmunotherapy, targeted therapeutics and chimeric antibody receptor cell therapy.



IN 2019, CLL GLOBAL RECEIVED \$1,864 IN DONATIONS FROM AMAZONSMILE THANKS TO CUSTOMERS WHO SELECTED CLL GLOBAL AS THEIR CHARITY OF CHOICE. DO YOU STILL HAVE GIFTS TO BUY THIS HOLIDAY SEASON? YOU CAN FEEL DOUBLY GOOD ABOUT YOUR GENEROSITY WHEN YOU SHOP AT AMAZONSMILE. JUST VISIT THE AMAZON SMILE WEBSITE ([HTTPS://SMILE.AMAZON.COM](https://smile.amazon.com)) AND SELECT CLL GLOBAL RESEARCH FOUNDATION AS YOUR BENEFICIARY. FOR ALL ELIGIBLE PURCHASES, THE AMAZONSMILE FOUNDATION WILL DONATE 0.5% OF THE PURCHASE PRICE TO CLL GLOBAL.



LOOKING FORWARD

With his retirement from patient care, Dr. Keating will now focus all of his energy and effort on CLL Global and CLL research. Along these lines, we are excited to host the next CLL Global Alliance Meeting on January 24-25th, 2020, where we bring together some of the brightest minds in CLL basic, translational, and clinical research to share their work and brainstorm new ideas. Immediately following the Alliance Meeting, we will host a meeting of the CLL Global Scientific Advisory Board (SAB). Based in part on presentations and discussions stemming from the Alliance Meeting, as well as what the SAB considers the most pressing needs and promising avenues of research in CLL, the SAB will help set the direction for CLL Global funding priorities in 2020. We look forward to sharing the outcome of both the Alliance and SAB Meetings, keeping you informed about the impact of your generosity on the greater CLL community.

In 2020, CLL Global will implement a board-approved restructuring of its administration. In order to give himself more time to focus on research, in his words, "the fun stuff", Dr. Keating will take on the title of CLL Global Founding Director. Dr. William Wierda, who many of you already know from the Leukemia Clinic at MD Anderson Cancer Center or one of his many scientific and/or educational presentations around the world, will take on the title of CLL Global President, overseeing much of the administrative responsibilities of the Foundation. This dynamic duo has been working together for almost 20 years, and Dr. Wierda has been an instrumental part of CLL Global since its inception. We look forward to continuing our work with Dr. Wierda in his new role as CLL Global continues to strive towards its mission of abolishing CLL as a threat to the life and health of patients by accelerating CLL research.

OUR IMPACT



Since 2008, CLL Global has committed **over \$27 million** towards CLL research



In 2019, CLL Global awarded **over \$2 million** to grant recipients in the U.S., Europe, Asia, and South America



CLL Global-funded researchers have published **over 290 manuscripts** across multiple disciplines



These articles have been **cited 15,868 times in 11,631 different manuscripts**, revealing the impact your dollars have on the CLL research community

HAPPY NEW YEAR

At this time of year, we think of days and times and you, our friends

*And pause in gratitude and love
To wish you well as this year ends*



All of us at CLL Global would like to wish you and your loved ones a happy holiday season and a healthy, prosperous new year. We are profoundly blessed to have the support of so many wonderful friends and benefactors who bring our dream of a finding a cure for CLL ever closer to reality. Recent advances in the development of targeted therapeutics and cellular therapies offer promise that, in the not-too-distant future, long-term, treatment-free remissions will be a real possibility for many patients with CLL.

Thank you for providing us an opportunity to support these promising advances, bringing them from the benchtop to the bedside.

CLL GLOBAL RESEARCH FOUNDATION:

OUR MISSION IS TO ABOLISH CLL AS A THREAT TO THE LIFE AND HEALTH OF PATIENTS BY ACCELERATING CLL RESEARCH.

Please consider making a donation today and help us turn our passion for finding a cure for CLL into a reality for patients around the world. To donate online, visit our website at cllglobal.org/donate. Donations may also be mailed to CLL Global Research Foundation, P.O. Box 301402, Unit 428, Houston, Texas 77230.