CLL GLOBAL RESEARCH FOUNDATION™

• CHRONIC LYMPHOCYTIC LEUKEMIA •

CLL RESEARCH

2025 Year In Review

CLL Global Research Foundation Has Provided Over $44M to Advance CLL Research (2005 – 2025).

Greetings!

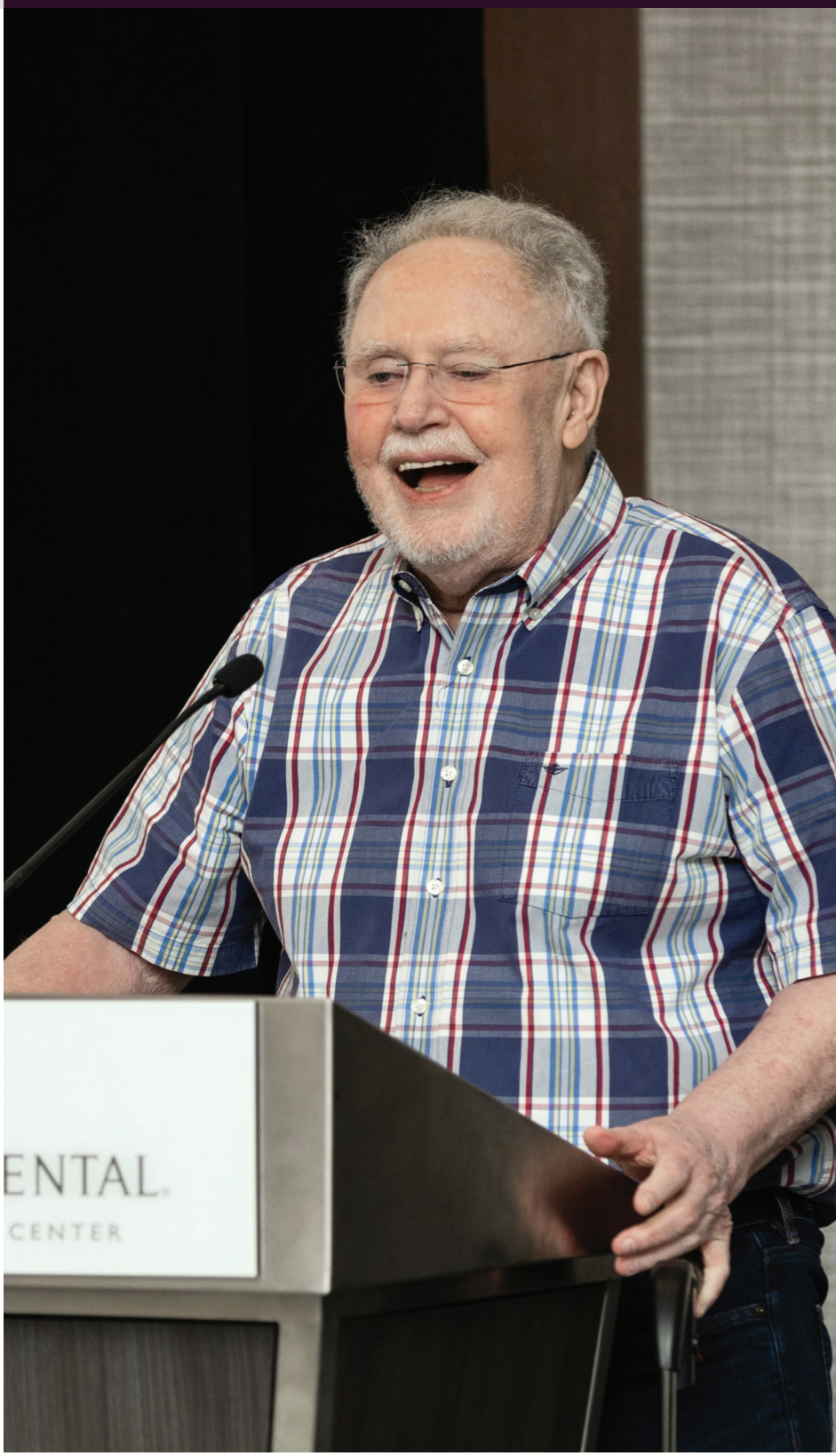
2025 has been an extraordinary year of progress—and of partnership—for all of us at CLL Global. Thanks to the dedication of our researchers, clinicians, patients, and supporters, we've seen breakthrough advances in targeted and time-limited therapies and gained new insights into the biology of CLL. These discoveries are expanding options for personalized, less toxic treatments and bringing us steadily closer to a cure.

This year also gave us meaningful opportunities to come together as a community. We celebrated the remarkable five-decade career of Dr. William Plunkett, whose pioneering work helped shape modern CLL research. Our spring Alliance Meeting gathered leaders in the field to share progress and tackle today's most pressing scientific challenges.

At our fall Virtual Town Hall, Dr. Catherine Wu highlighted the key questions that remain in CLL research. And in November, our inaugural Patient-Focused Research Symposium showcased how CLL Global–funded investigators are directly improving patient care and outcomes.

As we reflect on this remarkable year, we are inspired by the strength and generosity of our community—and more hopeful than ever about the future of CLL research.

Together, we are building the momentum needed to drive the next generation of CLL discoveries.



2025: A Year of CLL Breakthroughs

Biological Breakthroughs

Discovery	Insight	Key Takeaway
The Role of the Microenvironment	Research reveled how cells in the lymph node and bone marrow protect CLL cells, helping them evade treatment	Targeting the support system around CLL cells may be as important as treating CLL
CLL-Derived Exosomes Influence Disease Progression	CLL cells release tiny particles called exosomes that reprogram surrounding immune and support cells, weakening the immune response and promoting CLL growth	Blocking exosome signaling could become a new therapeutic strategy to prevent relapse or resistance
PD-1 Found on CLL Cells – Not Just T-Cells	A surprising finding showed that CLL cells can express PD-1, a marker linked to T-cell exhaustion and immune dysfunction	May lead to new immunotherapy approaches tailored to novel CLL biology
New High-Risk CLL Subtypes Identified	Rare genetic subgroups with distinct biology including stronger B cell receptor signaling and drug resistance characterized	A better understanding of rare CLL variants allows more personalized care and earlier intervention
Genetics and the Microenvironment Drive Resistance	Resistance to BTKi and BCL2i is driven not just by genetic mutations but also support from the microenvironment during treatment	Future therapies will need to combine agents that disrupt the microenvironment to prevent resistance

Clinical Breakthroughs

Trial / Study	What Was Studied	Key Takeaway
FLAIR	Compared ibrutinib (I) alone versus I + venetoclax (V) versus chemoimmunotherapy (CIT) in untreated CLL	I+V provided deeper, long-lasting remission, allowing many patients to finish therapy and remain in remission
AMPLIFY	Acalabrutinib (A) + V with or without Obinutuzumab (O) in untreated CLL	A+V showed strong results as a first-line, time-limited therapy showing potential as new frontline standard. FDA review of combo underway.
BRUIN CLL-314	Compared next-generation BTK inhibitor (BTKi), Pirtobrutinib, versus I in untreated CLL	Pirtobrutinib demonstrated excellent outcomes with fewer side effects offering alternative to older BTKi's
NX-5948 BTK Degrader	First-in-class BTK degrader tested in relapsed / refractory (R/R) CLL	New drug class targeting treatment-resistant CLL provided meaningful responses in patients with few remaining options
MRD-Guided I+V	Fixed-duration I+V with minimal residual disease (MRD)-guided treatment stopping in R/R CLL	Using MRD to guide ending treatment reduces side effects, healthcare costs and total time on therapy

Significant progress in 2025 is reshaping both our understanding of CLL and how it is treated. Researchers uncovered new insights into the CLL microenvironment and exosomes, key factors that help leukemia cells survive, and which may contribute to relapse. They also identified PD-1 expression, usually associated with T-cells, on CLL cells, as well as new high-risk biological subtypes, paving the way for more effective personalized care.

On the clinical front, momentum continued toward shorter, targeted, and less toxic treatment. Time-limited combinations such as ibrutinib + venetoclax (FLAIR) and acalabrutinib + venetoclax (AMPLIFY) achieved deep, lasting remissions. Emerging approaches, including pirtobrutinib, BTK degraders, and MRD-guided treatment decisions, are helping more patients achieve remissions and go off treatment.

CLL Global collaborators and grantees feature prominently among the authors of these remarkable developments. Together, these advances strengthen hope for longer-lasting remission and a future cure. Their work highlights the power of collaboration and the impact that focused, patient-driven research can achieve.

A TRIBUTE TO DR. WILLIAM PLUNKETT

Dr. William (Bill) Plunkett has devoted five remarkable decades at MD Anderson to advancing leukemia research, transforming care for patients with CLL and other blood cancers. His longtime collaboration with our founder, Dr. Michael Keating, helped bridge laboratory discoveries to real patient impact and set a new standard for translational research excellence. Together, their partnership laid the foundation for many of the breakthroughs that continue to guide modern CLL therapy today.

Admired not only for his scientific brilliance but also for his kindness and mentorship, Dr. Plunkett has inspired generations of scientists and clinicians. His work has touched countless lives and helped shape CLL Global into a leader in advancing new therapies. Dr. Plunkett continues his service to the CLL community as a member of the Scientific Advisory Board and the Board of Directors for CLL Global.

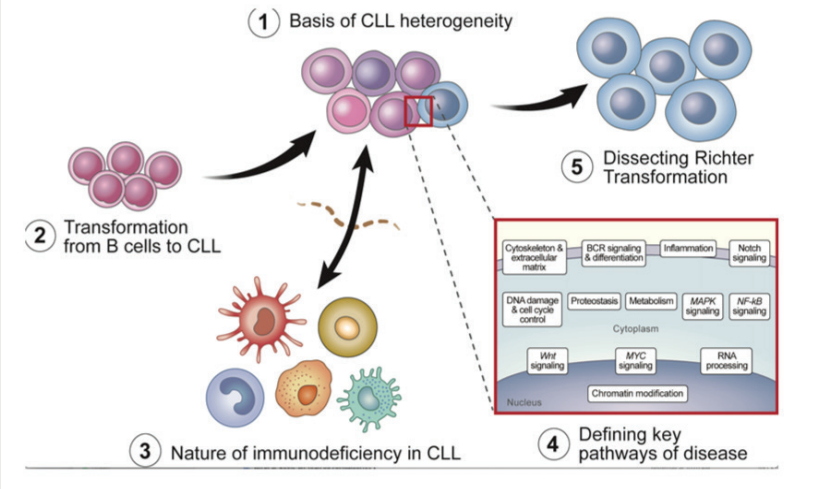
We are deeply grateful for his dedication and wish him a joyful, well-deserved retirement.

Dr. Bill Plunkett (left) and Dr. Michael Keating celebrating 50 years of CLL translational and clinical research collaboration.

Follow us on Facebook to keep abreast of the latest CLL news and to find out about upcoming events.

CLL GLOBAL TOWN HALL

In October, CLL Global hosted our second Virtual Town Hall of the year with guest speaker Dr. Catherine Wu, Chief in the Division of Transplant and Cellular Therapy at Dana-Farber Cancer Institute. While acknowledging the extraordinarily promising era of therapeutic options now available to patients, Dr. Wu also underscored the key questions that must be answered to fully realize precision oncology, including:



Areas of unmet need in CLL research. Image credit: Dr. Catherine Wu.

1. Why CLL cells differ and why some survive treatment
2. How CLL begins, and whether early intervention could change its course
3. Immune dysfunction in CLL and how to restore it after treatment
4. New pathways driving CLL, leading to future treatment options
5. Richter's transformation, why it happens, and how to prevent it

Dr. Wu emphasized that today's advanced scientific tools are bringing us closer to more personalized, effective, and less toxic treatments for every CLL patient. You can view the full presentation on our website at cllglobal.org/upcoming-events.

PATIENT-FOCUSED RESEARCH SYMPOSIUM

Dr. George Calin

On Friday, November 14, CLL Global hosted our inaugural Patient-Focused Research Symposium, showcasing innovative research made possible through grant funding from CLL Global. Eight investigators representing basic, translational, and clinical science shared how their work is advancing patient care and outcomes.

For many attendees, it was a rare chance to hear directly from the scientists whose work is shaping the future of CLL treatment. The presentations underscored just how rapidly the field is evolving—and how much promise lies ahead.

A meaningful highlight was the opportunity for presenters to thank patients directly for their essential role in making progress possible. By donating blood and tissue samples for research and participating in clinical trials, patients make new discoveries possible. As Dr. George Calin shared, "we honor the strength of our patients and families whose generosity fuels the search for cures!"

The event also showcased the collaboration needed across the CLL community - from drug discovery, to translational science, to clinical trials and therapy development - and the central role of patients in every breakthrough.

You can view the presentations on our website at cllglobal.org/upcoming-events and stay updated on future symposiums.

Together, these efforts are bringing us closer to safer treatments, deeper remissions, and a future free from CLL.

Thank You

CLL Global was founded on a powerful partnership among motivated patients, visionary clinicians, and pioneering scientists united in the mission to cure CLL. The impact of this collaboration is clear—we have never seen more progress, more therapeutic options, or more hope for the future.

Yet alongside these remarkable advances, this past year has also brought new challenges and uncertainties for research. It is essential that these obstacles do not slow our momentum. As federal cancer research funding increasingly shifts toward other priorities, your partnership has never been more vital to ensuring that lifesaving CLL research continues to advance. With your continued support, we can sustain the progress that is transforming care for patients today and accelerating the discoveries of tomorrow.

As we close out this remarkable year, we are deeply grateful for your trust, generosity, and shared commitment to a future free from CLL. Wishing you and your loved ones a warm and joyful holiday season and a healthy, hopeful New Year.

Our mission is to abolish CLL as a threat to the life and health of patients by accelerating CLL research. Find out more about us by visiting our website at www.cllglobal.org.

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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, c/o Dr. Michael Keating, P.O. Box 301402, Unit 428, Houston, Texas 77230.

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