



• CHRONIC LYMPHOCYtic LEUKEMIA •

CLL RESEARCH

2022 Mid-Year Update

CLL Global has provided over \$33 million in research funding (2005-2022).

Greetings!

In this newsletter edition, we are excited to share with you some of the accomplishments that CLL Global Research Foundation has achieved in the first half of 2022, the highlight of which was hosting the CLL Global Alliance Meeting in person for the first time in two years! Also noteworthy, our Scientific Advisory Board (SAB) has been hard at work setting priorities for future research investments based on several critical areas of unmet need in CLL. Two newly funded projects reflect these efforts, and we will share with you how CLL Global carefully stewards its finances, maximizing the impact of each donation we receive. We also highlight the CLL Global-funded work of Drs. Rong Chen and William Plunkett, whose efforts in basic and translation science have led to the opening of a promising Phase I/II, multi-center clinical trial. You can find out more about the latest CLL clinical trial updates and get your questions answered by CLL experts at our June 28th virtual Town Hall. And last but not least, we ask you to join us in wishing our founder, Dr. Michael Keating, and our president, Dr. Bill Wierda, the happiest of birthdays on July 1st and July 4th, respectively.



From left to right: Drs. Zeev Estrov, Michael Keating, and George Calin hard at work finding a cure for CLL.

CLL Global Alliance Meeting

Each year, CLL Global hosts the Alliance Meeting, which brings together experts from around the world to share their research and foster collaboration across disciplines. After a two-year hiatus due to restrictions imposed by the COVID-19 pandemic, we were excited to gather in person on April 28-29, 2022, in Houston, Texas. Reflecting our commitment to advance outstanding CLL research, the presentations covered a range of topics whose understanding is essential to curing CLL.

These topics included dissecting the biology of CLL cells and how their interactions with support cells in the bone marrow and lymph nodes - the microenvironment - promote CLL cell survival. Also presented were data on the discovery of new therapeutic targets to overcome drug resistance and attack CLL cells, as well as novel treatments for high-risk, relapsed, and refractory patients. We also learned how integrating multiple layers of molecular and genetic information about an individual's CLL can help bring precision medicine to patients. Our goal moving forward is to build on the momentum fueled by our research partners to make curing CLL a possibility for all patients.

Grant Selection PROCESS

Ever wonder how CLL Global grant recipients are selected? Always mindful of our fiscal responsibility to our donors, we have a multi-step review process that ensures only the most promising research is funded.

FUNDING PROCESS

Scientific Advisory Board (SAB) sets funding priorities highlighting unmet needs in CLL.

Applications recommended for funding reviewed internally by SAB.

Investigator notified of award and research initiated.

Request for Applications

Application Submission and External Review

Internal Review by SAB

CLL Global Board of Directors

Grant Awarded

Applications sent to external expert reviewers for comment and recommendation for/against funding.

Board of Directors oversees final review and funding determination.

FROM BENCH TO BEDSIDE

It takes years of discovery and development for a drug to be approved for use in human clinical trials, and most never make it that far. Thanks in large part to the extensive research efforts of Dr. William Plunkett, Professor, and Dr. Rong Chen, Assistant Professor, Department of Experimental Therapeutics, MD Anderson Cancer Center, a Phase I/II, multi-center clinical trial of fadraciclib (Cycacel) for use in subjects with leukemias, including CLL, has recently opened (NCT05168904). Fadraciclib is a drug that selectively inhibits two enzymes called CDK2 and CDK9. Drs. Plunkett and Chen showed that inhibition of CDK9 caused depletion of Mcl-1, a key survival protein that sustains CLL cells, and that depletion of Mcl-1 resulted in CLL cell death.*

They further showed that combining fadraciclib with venetoclax (Venclexta), which inhibits the other key CLL survival protein, Bcl-2, further enhanced CLL cell death including in cells from high-risk patients.

Cyclin-dependent kinase inhibitor fadraciclib (CYC065) depletes anti-apoptotic protein and synergizes with venetoclax in primary chronic lymphocytic leukemia cells

Chen, Rong^a; Chen, Yuling^a; Xiong, Ping^a; Zheleva, Daniella^b;
Blake, David^b; Keating, Michael J.^c; Wierda, William G.^c;
Plunkett, William^{a,c} ✉

*Chen et al. 2022. *Leukemia*. Cyclin-dependent kinase inhibitor fadraciclib (CYC065) depletes anti-apoptotic protein and synergizes with venetoclax in primary chronic lymphocytic leukemia cells. (<https://doi.org/10.1038/s41375-022-01553-w>)

The clinical trial will test the safety and efficacy of fadraciclib in CLL patients who have progressed on two or more therapies, as well as the combination of fadraciclib plus venetoclax in CLL patients who have progressed after therapy with venetoclax. CLL Global is thrilled to partner with Drs. Plunkett and Chen on this ground-breaking research.



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

UNMET NEEDS

Thanks to the remarkable progress that has been made in therapy and outcomes for CLL, there is the real potential for many patients to be cured with a finite duration of therapy with a Bruton tyrosine kinase (BTK) inhibitor and venetoclax. Longer term follow-up of these clinical trials will hopefully confirm its curative potential, and the regimen is expected to receive FDA approval in the near future. There are, however, still several critical areas of unmet need in CLL that must be addressed to safeguard the health and well-being of patients. The CLL Global Scientific Advisory Board (SAB) meets several times a year to review these areas of unmet need and to advise on how best to address them. The figure below outlines our current priorities.

Survivorship

- Immune Dysfunction
- Infections
- Vaccination Efficacy
- Second Cancers

Richter's Transformation

- Understand Drivers
- Identify Biomarkers
- Develop Effective Therapies

Refractory CLL

- Understand CLL Clonal Evolution
- Optimize Current Therapies
- Develop New Therapeutics

ADVANCES IN CLL

June 2022 offers a plethora of information on the latest advances in CLL with two premier scientific conferences scheduled. The American Society of Clinical Oncology (ASCO) meeting is being held June 3–7 in Chicago, IL. The theme of this year's meeting is *Advancing Equitable Cancer Care Through Innovation*. The European Hematology Association (EHA) Congress, celebrating its 30th anniversary, is being held June 9–17 in Vienna, Austria. Both conferences will provide information on new clinical trials as well as longer term follow-up of ongoing trials. Highlights from both conferences will be presented at our next virtual Town Hall.



2021 ASCO[®]
ANNUAL MEETING
#ASCO21

Virtual Town Hall

Join us on Tuesday, June 28th, 2022, from 1-2 PM CT for our next virtual Town Hall. CLL Global President, Dr. Bill Wierda will provide an update on the latest CLL clinical trial results presented at the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) meetings held earlier in the month. You will also hear from Dr. Jennifer Woyach, Professor, Division of Hematology, The Ohio State University, on how funding from CLL Global is helping her develop new therapies for patients with genomic high-risk CLL. Of course, CLL Global founder and friend to all, Dr. Michael Keating, will be joining the discussion, and the entire expert panel will answer your questions. Don't miss this opportunity to get up to speed on the rapidly evolving CLL treatment landscape. Visit our website at cllglobal.org and click on "Upcoming Events" to register. Registration is free!



A BRIGHTER FUTURE AHEAD

Thanks to the dedication, tenacity, and resolve of an international army of scientists and health care professionals, the majority of patients newly diagnosed with CLL will live a normal life span. Ongoing clinical trials suggest this can be achieved with a finite duration of therapy, the optimal combination(s) of which are currently being explored. There are, however, fundamental issues for CLL patients that must be addressed.

These include the immune dysfunction inherent to the disease and exacerbated by certain therapies which result in patients having an increased risk of infections, second cancers, and a reduced response to vaccines intended to protect them from disease. There are patients who are or become refractory to current therapies, and we have very few therapeutic options for patients who develop Richter's Transformation. CLL Global has been a driving force in the transformation of CLL therapy, and we continue these efforts as we tackle the unmet needs of current and future CLL patients. Thank you for making it possible for us to pursue our mission of abolishing CLL as a threat to the life and health of patients.

Happy Birthday

Please join us in wishing Dr. Michael Keating (July 1st) and Dr. Bill Wierda (July 4th) a very happy birthday! This year, we would like to ask a small favor of all of you who know and love Dr. Keating. Dr. Keating has been retired from the clinic for several years now, and he dearly misses seeing his patients. For his birthday this year, we want to make a poster of well wishes from his patients and friends that Dr. Keating can hang on his wall. Please email your message to townhall@cllglobal.org. It will be the perfect gift!



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**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.