At the current moment, we are enjoying a flurry of space-inspired movies, i.e. Star Wars. This engenders futuristic musings which have me thinking of a cure for CLL in terms of the trajectory of rocket travel. For instance, sending a rocket to the moon has a relatively short timeline before landing is achieved and success declared. Such a trip is measured in days, whereas a journey to Mars requires an extended timeline of months rather than days and so demands greater patience on the part of astronauts, scientists and the rest of us. Curing CLL can be thought of as a metaphorical timeline that is not as near as a trip to the moon, but not as far away as a trip to Mars. We have immediate access to the product of thirty years of research and also have the long term anticipation of future knowledge.

The present era of CLL is grounded in years of study and research. The current status of CLL is considered to have commenced in 1983 when fludarabine was found to be effective for management of relapsed and refractory CLL. The evolution of fludarabine-based treatments inspired the fludarabine-cyclophosphamide-rituximab (FCR) regimen, which has now been approved as the standard of treatment in the United States and around the world for patients less than 65 years of age with relatively good physical condition.

However, treatment has continued to evolve with the development of new drugs which have ushered in a new era of personalized medicine for the treatment of CLL. The first drug, recognized approximately 7 years ago, was idelalisib, followed shortly thereafter with ibrutinib. Both of these targeted specific enzymes in the B lymphocyte signaling pathway and have been approved by the FDA for management of varying stages of CLL, including relapsed and refractory CLL. Approximately four years ago, interest developed in another drug called venetoclax. Venetoclax inhibits a different protein in the signaling pathway and is recognized as an exciting new drug that rapidly depletes CLL, particularly in the bone marrow and to a somewhat lesser extent, in the lymph nodes. These investigations have continued to be explored with great success and are now FDA approved for the management of patients with a particularly difficult-to-treat form of CLL in which there is loss of part of chromosome 17 or the leukemic cells have a mutation in a protein called P53. Additionally, rituximab, a monoclonal antibody, has become a cornerstone of many treatment regimens for leukemia and lymphoma, while a new form of monoclonal antibody that attacks the same target as rituximab, obinutuzumab, has been shown to be an even more effective treatment for CLL. Thus, we now have multiple drugs which may be used sequentially or in combination based on the needs of the individual patient. There are many clinical trials currently testing these options as well. With these therapies we can consider that we have initiated the long voyage to Mars and that we are waiting to see if success will manifest itself when a portion of patients who are potentially cured of the disease is significantly increased to a level higher than we have previously been able to achieve.
Our target is to improve the overall survival of patients free of disease for more than 10 years. With the FCR program, 30-40% of patients are in this category, with the most significant success experienced by those below the age of 70. This percent or better is a target that the new regimens of drug combinations will have to achieve. Early results of clinical trials are very promising in that they are effective in eradicating detectable evidence of CLL within 12-18 months after initiation. It is extremely important, however, to identify what subsets of patients are being affected most favorably. A key to this determination is what is called the mutation status of the patients. This status is determined by the presence of a mutation in the gene which makes antibodies against infection, the IGHV gene. The more mutated this gene is, the better the outcome with regimes such as FCR. The other key group of patients are those who have lost a part of chromosome 17, or who have a mutation of the P53 gene. These cases are very difficult to treat with FCR. However, even with these difficult to treat patients, we have dramatically improved quality of life and survival outcomes with the use of new agents such as ibrutinib and venetoclax. Studies for frontline treatment of younger patients with these new, non-chemotherapy based drugs are already launched and tracking the long term outcomes of these trials will be especially important in the analysis of their success.

So what about the present patients who are undergoing treatment but still have residual disease? Eradication of the residual disease is a necessity for long term freedom from recurrence of CLL. Three major initiatives are underway to address this concern. The first of these uses venetoclax to mop up remaining abnormal cells in the bone marrow. There are studies in patients who have been on ibrutinib and achieved a very good clinical response but who still have residual disease (MRD positive). A hopeful option for these patients is the utilization of a DNA vaccine against a protein called telomerase (hTERT). This study will be initiated in January 2018 and we hope to have early results within a one year time frame. Another exciting development has been that of the CAR-T cells. While effective, use of CAR-T technology is expensive and cumbersome. A new initiative using a variation of CAR-T cells, CAR-NK cells, which use Natural Killer cells isolated from cord blood, is being developed. The DNA vaccine and CAR-NK studies are being strongly supported by the CLL Global Research Foundation as keys to building curative strategies. The other groups that are being evaluated for new treatment strategies are the “watch and wait” patients, particularly those who are likely to need treatment within three years. There are studies underway looking at the use of chemotherapy in combination with ibrutinib or the DNA vaccine for this population. Patients over the age of 70 will need particular attention. We need treatment options which are likely to be beneficial in not only prolonging life but also improving the long term quality of life in these patients. It is also important for us to note that when clinical trials are conducted, they are usually conducted on younger patients. This has particular significance for CLL patients whose average age of diagnosis is 72 years of age.

The evolving options make this a very exciting time in CLL research. You will be pleased to know that the CLL Global Research Foundation is at the forefront of supporting many of these activities and translating the optimistic early information into programs that have benefits for present-day CLL patients.
RESEARCH: ALLIANCE WORKING GROUPS

In our 2016 Year in Review publication, we told you about the establishment of our Microenvironment Working Group, introducing you to the investigators and detailing their research plans. We have continued to expand our Working Groups in 2017, funding an ambitious project in Melbourne, Australia, as well as an innovative new immune reconstitution project. Keep reading to learn about some of the recent accomplishments of our Microenvironment investigators as well as details of our new initiatives.

MICROENVIRONMENT WORKING GROUP: Year 1 Progress

Principal Investigator: Nicholas Chiorazzi, MD
Institution: Feinstein Institute for Medical Research – North Shore LIJ Health Systems, Manhasset, NY

Deciphering crosstalk between leukemic B cells, T-cell subsets, and myeloid-derived suppressor cells in the tissue microenvironment to develop novel therapies for CLL

CLL B lymphocytes require inputs from other normal white blood cells to survive and grow. In this study we are analyzing the inputs received from T lymphocytes, in particular the T helper cell 17 subtype (“Th17 cells”), and from myeloid-derived suppressor cells on the survival and growth of CLL B lymphocytes. Over the past year, we have made two observations that impact on our understanding of CLL disease development and progression. First, we have found that CLL B cells alter the ability of a patient’s bone marrow to make Th17 cells. This is important since our second finding is that products of Th17 cells can limit the survival of CLL cells. This is consistent with our earlier findings that patients with high numbers of Th17 cells have a better clinical course and longer survival. We will investigate these two issues in more depth in 2018 in hopes of identifying ways to increase the apparent benefit to patients by increasing the numbers of Th17 cells.

Principal Investigator: Sabrina Bertilaccio, PhD
Institution: MD Anderson Cancer Center, Houston, TX

Targeting the Monocyte/Macrophage Lineage as a novel therapeutic strategy in CLL

CLL is the most frequent adult leukemia in the western world, due to the accumulation of mature neoplastic B lymphocytes. Despite the use of intensive immuno-chemotherapeutic treatments, CLL is still an incurable disease. Given that extensive studies demonstrate how leukemic development and expansion correlate with microenvironmental stimuli delivered by nonmalignant 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 the leukemic progression and dissemination is poorly understood. Therapeutic approaches aimed at targeting the monocyte/macrophage-CLL cell interaction are under evaluation. We integrated different approaches shuttling between human primary cells and animal models to investigate the molecular mechanisms that regulate cellular cross talk between leukemic and monocyte/macrophage lineage cells during leukemia progression. Overall these approaches allowed: a) to understand the cellular and molecular dynamics of leukemic cell monocyte/macrophage interactions that occur during leukemia progression and b) to validate trabectedin, an innovative therapeutic approach aimed at targeting the monocyte/macrophage lineage.
CENTRE OF RESEARCH EXCELLENCE IN CHRONIC LYMPHOCYTIC LEUKEMIA AT THE VICTORIA COMPREHENSIVE CANCER CENTRE

Principal Investigator: Constantine Tam, MBBS, MD, FRACP, FRCPA
Institution: St. Vincent’s Hospital and Peter MacCallum Cancer Center, Melbourne, Australia

In the summer of 2017, CLL Global Research Foundation funded an ambitious research program, the “Center of Research Excellence in Chronic Lymphocytic Leukemia at the Victorian Comprehensive Cancer Centre (VCCC, pictured above)”. Headed by Dr. Constantine Tam of the Peter MacCallum (Peter Mac) Cancer Centre and the University of Melbourne, located in Melbourne, Victoria, Australia, this research program seeks to expand on the major advancements that have occurred in the treatment of CLL. The project focuses on seven research areas: 1) development of an invasive-free assay using circulating tumor DNA to track minimal residual disease; 2) understanding cardiotoxicity associated with BTK inhibitors (BTKi) such as ibrutinib; 3) understanding BTKi associated bleeding disorders; 4) investigating cellular events before and after treatment begins, and at the time of relapse; 5) defining the impact of active CLL and novel therapies on host immunity; 6) expanding small molecule inhibitor combination programs, i.e. ibrutinib and venetoclax; 7) developing activated B-CLL as an antigen presenting cell for immunotherapy.

Six Month Update from Dr. Tam

New, innovative studies including the combinations of ibrutinib and venetoclax, BGB-3111, and PD1 inhibitors, were added to our serial blood sampling studies with the aim of finding out how these drugs impact on the ability of CLL to mutate and escape our treatments, and to study how these drugs may impact on the normal immune system of the patient. The latter research will be conducted by Dr. Sasanka Handunnetti, who has optimized a 26 color flow cytometry panel to study in detail individual immune cell subsets in blood. The plasma DNA project is progressing well with the appointment of Dr. Kah-Lok Chan whose PhD project will revolve around the further development of this technology in CLL – our initial pilot results were very well received, being published in Nature Communications this year. With regards to cardiotoxicity of BTK inhibitors, the Foundation’s generous funding has permitted the initiation of a suite of detailed cardiac studies (including exercise MRI) in patients starting BTK inhibitor therapy, led by Dr. Chloe Tang. In the laboratory, Dr. Julie McMullen has discovered that mice predisposed to heart disease had increased rates of atrial fibrillation when given ibrutinib, mimicking the situation in humans; further experiments are currently being conducted to determine why this happens. Dr. Denise Jackson is leading our work on determining why patients taking ibrutinib are predisposed to bleeding and has made some new and exciting findings regarding the molecules that assist platelets to attach to bleeding sites; further experiments are ongoing. Collectively, the CLL research program at VCCC thank CLL Global Foundation for its generous support and we look forward to updating the Foundation on our progress at the research meeting.
On January 20-22, 2017, CLL Global sponsored our annual Alliance Meeting on the campus of MD Anderson Cancer Center in Houston, Texas. The theme of this year’s meeting was ‘How Will My Research Impact CLL within 2 Years?’. Over forty attendees from three different continents participated in this unique gathering of clinicians and research scientists, all of whom are experts in CLL committed to finding a cure, sooner rather than later. Topics discussed at the conference included the CLL microenvironment, CLL genetics, therapeutic development, immunology and immune restoration in CLL, and minimal residual disease as a surrogate for treatment efficacy. The small, intimate atmosphere of the Alliance meeting offered participants the opportunity for open discussion, brain storming and collaboration, all with the shared goal of advancing CLL treatment options and improving the quality of life for all CLL patients.

Drs. William Plunkett, Federico Caligaris-Cappio, and Jan Burger (front row, left to right) at the CLL Global Alliance Meeting on January 21, 2017.
Thanks to Our Benefactors

Over the last eleven years, CLL Global Research Foundation has provided over $26 million to fund cutting edge research aimed directly at improving the quality of life of patients with CLL, expanding personalized treatment options, and finding a cure for the disease. To date, we have funded over 80 individual investigators, both new and established, in over 15 countries throughout the world, truly living up to the ‘Global’ aspect of our name. This investment has resulted in 252 peer-reviewed publications that have been cited almost 11,000 times. This publication success often translates into investigators and institutions receiving further funding from additional public and private funding sources - meaning your donation is parlayed several-fold into additional research dollars. We are already seeing this success translate into new, FDA-approved treatment options for CLL patients, with many more on the horizon.

Fly for a Cure

We are constantly amazed at the creativity of our patrons in finding ways to support the mission of CLL Global Research Foundation. From golf tournaments, to art auctions, to concerts, we have been the fortunate recipients of their generosity. This year was no different. On April 9, 2017, the Eyad Karkoutly Lymphoma Leukemia Research Foundation held the ‘Fly for a Cure’ fundraising event at the Spirit Ranch in Lubbock, Texas. This kite flying fundraiser included kites of all sorts, local food trucks, live music, and even peacocks wandering about. Proceeds from the event, totaling $18,000, were presented to CLL Global Research Foundation president Dr. Michael Keating, who expressed his gratitude and appreciation for their charity, committing the funds to support ongoing CLL research.
In 2017, we continued our commitment to bringing the most up to date information to CLL patients and their loved ones.

On Saturday, February 18, 2017, we, along with our production partners at Patient Power, hosted a town meeting at the MD Anderson Cancer Center in Houston, Texas. Over 400 people attended the event in person and online. Speakers included CLL Global’s very own President and CEO, Dr. Michael Keating, in addition to Dr. Nicole Lanman, Associate Clinical Professor of Medicine at Columbia University Medical Center, Dr. Wenli Liu, Associate Professor, Integrative Medicine Program, MD Anderson Cancer Center, and patient advocate Jeff Folloder. The event hosted by Andrew Schorr, Patient Power co-founder, two-time cancer survivor, and patient advocate. The conference covered many topics relevant to CLL patients including clinical trials and how to get involved, strategies for managing CLL symptoms and side effects, and resources for living life to the fullest with CLL. Stay tuned for more live, online education events with Dr. Keating throughout the year.

A second town meeting was held on Saturday, September 23, 2017. CLL Global, in conjunction with Patient Power, The US Oncology Network, Compass Oncology, and Willamette Valley Cancer Institute and Research Center, hosted the education event, ‘Expanding Treatment Options for CLL – A Town Meeting for Patients, Their Families, and Caregivers’. The event, which offered participants the opportunity to learn about emerging therapies, current treatment options, and support resources, was held at the Embassy Suites in downtown Portland, Oregon. Panel participants included CLL Global Research Foundation president Dr. Michael Keating. Over 100 people attended in person and an additional 142 participated online. A question and answer session was available to both in person and online participants and, as always, registration was free. Planning for the next CLL education event, being held in Houston, Texas is underway. Check out our website and Facebook page for more information on future town meetings.
Looking Ahead

The New Year is already shaping up to be a busy and productive one. On January 19-22, 2018, CLL Global will hold our next Alliance Meeting at MD Anderson Cancer Center in Houston, Texas. Highlights from the meeting will be shared in our bi-monthly newsletter and on our Facebook page. On March 24, 2018, the next CLL patient town hall, co-hosted with our production partner Patient Power, will be held at MD Anderson Cancer Center. This in-person and live broadcast event, entitled “Making Empowered Decisions: Understanding Your Options to Get the Best CLL Treatment”, is free to attend but registration is required. Information on registration will be made available on our website, cllglobal.org. Planning for a second town hall event, to be held in Seattle, WA, sometime in the fall of 2018, is also underway. In addition, the second annual Fly for a Cure event will be held on April 8, 2018, in Lubbock, Texas. We look forward to sharing these experiences, and many more, with you over the course of the year.

CLL Global Research Foundation:

Our mission is to abolish CLL as a threat to the life and health of patients by accelerating CLL research.

Even as we celebrate at the end of the year at hand,

We anticipate the peace and healing

that the new year offers.

Your generosity makes both

celebration and anticipation possible.

We wish you the joy of the season

and hope for things to come.

Happy New Year

CLL Global Research Foundation would like to take this opportunity to wish everyone a joyful holiday season and a prosperous and productive New Year. We are profoundly grateful for your continued support, and are committed to putting your donations directly into cutting-edge CLL research and patient support endeavors. Over 90% of our annual expenditures go directly towards these priorities. The upcoming year holds great potential to bring more, improved treatment options for CLL patients. We look forward to sharing these exciting best practice advances with you throughout the year.

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 please visit www.justgiving.com/cllglobalresearchfoundation. Donations may be mailed to CLL Global Research Foundation, P.O. Box 301402, Unit 428, Houston, Texas 77230.