CLL GLOBAL RESEARCH FOUNDATION®
• CHRONIC LYMPHOCYTIC LEUKEMIA •
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CLL RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – A PROGRESS UPDATE

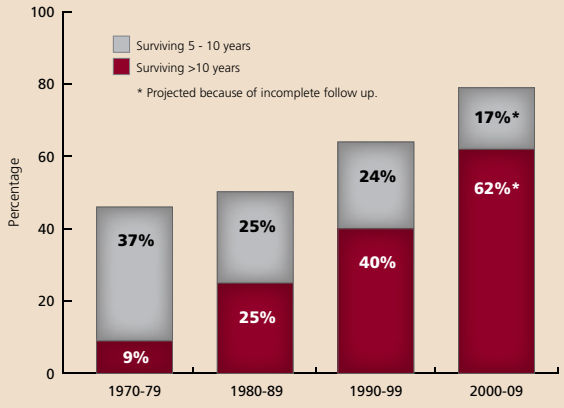
ISSUE 2-2011

ALL KNOWLEDGE IS historical

A great man and my mentor, Dr. Emil J Freireich, always told me that "all knowledge is historical". This is obviously true because we draw conclusions from observing, recording and analyzing what we have seen in the recent and distant past. I am often questioned by my colleagues about the time I spend maintaining a database of all chronic lymphocytic leukemia (CLL) patients coming to MD Anderson. Indeed it is very time consuming to work on the database, but something is learned from every person whose data is entered.

We now have a wealth of information which helps us identify common patterns of progression, response and various complications. We better understand the significance of prognostic factors in the course of CLL and how patients may respond to a particular treatment. Comparisons can also be made between different treatments. Statistical analyses from the database are provided for peer-reviewed articles in scientific journals, presentations and clinical research.

CLL 5 Year + 10 Year Survival by Decade



MD Anderson Cancer Center CLL Database

While many aspects of CLL are better understood, many others remain to be determined. There is some concern at the present time about the likelihood of patients developing second cancers as a consequence of, or in association with, a variety of treatments. Without having accurate documentation, it is impossible for us to know if there is a correlation, or if the disease itself causes second cancers. Long term follow-up is necessary, but this can be cumbersome for both patients and physicians.

It is clear from the data compiled over decades that there has been a significant survival improvement for CLL patients. Has a change in the natural history of CLL altered the survival curve? It is more likely that better treatments are responsible for improving the outcome and longevity of patients. In the figure you will note the improvement in five and 10 year survivals that have occurred over various decades. It is abundantly clear that we not only have a substantial number of patients that are living for very long periods of time, but many of them have been free of any recurrence of their leukemia for 10 years or more.

The improved survival gives us reason to celebrate. Gaining this knowledge creates more questions and new goals. If CLL patients are living longer, can their immune systems be improved so that they will have a better quality of life? Many years ago, the goal was simply to get patients in remission. The current goal is for people to live a long vibrant life full of opportunity and free from consequences of the disease. The ultimate goal is obviously a cure.

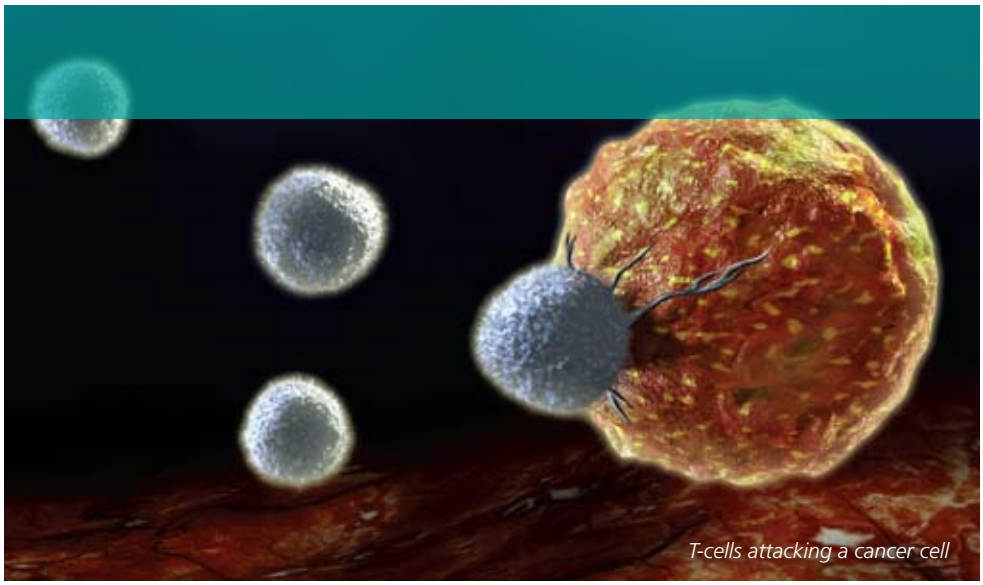
Some of what I learned in medical school is no longer relevant. Certain things taught to the current medical students will be obsolete in a matter of time. This does not mean that education is a waste of time. On the contrary, historical knowledge has to be applied to the current circumstances in order to develop the next generation of knowledge. Historic data guides researchers to answers and subsequent questions, and provides patients information on what to expect from their disease and from treatments. I now have a very substantial historical perspective and an AARP card to prove it. I will continue to use this perspective to create new knowledge. ::

Dr. Michael J. Keating

Dr. Michael Keating, Professor of Medicine at MD Anderson Cancer Center, serves as president and CEO of the CLL Global Research Foundation. He is an internationally renowned CLL clinical scientist dedicated to patient care and to development of potentially curative CLL therapies.

inside this issue:

CAR research SPEEDS AHEAD



T-cells attacking a cancer cell

Automobiles are made in factories in Detroit and around the world to meet the demand of people who want to drive in style. So why are scientists in laboratories competing to invent new cars? The cars they are working on are chimeric antigen receptors (CARs). These CARs are genetically attached to the surface of T-cells, which are circulating immune cells that protect the body from infection. CARs are engineered to persuade the T-cells to seek out certain proteins. All cells have proteins specific to the cell type. B-cells, including CLL cells, express a number of proteins on their surface such as CD19, CD20 and CD23.

CLL is a type of B-cell malignancy. The first CARs being used to target B-cell malignancies have been programmed against the surface protein CD19. These CD19-specific CARs have been investigated extensively over the last few years. You likely have seen news coverage of positive results from the University of Pennsylvania study led by Drs. Carl June and Bruce Levine.

This CAR has proven successful with dramatic initial responses in three CLL patients. Both healthy and malignant B-cells express CD19, so the healthy cells are also targeted by this CD19-specific CAR. The depletion of healthy B-cells is being counteracted with IVIG therapy. Results from the UPenn study are still preliminary and more data is needed to determine duration of response. CLL Global has supported other research projects of Drs. June and Levine, but not the recently publicized research.

A number of other CLL Global investigators have also been developing the CAR concept, including collaborators at Baylor College of Medicine in Houston, Texas with Dr. Gianpietro Dotti being the principal investigator. CLL Global grant recipient Dr. Renier Brentjens at Memorial Sloan-Kettering is also currently evaluating a CAR against CD19. Dr. Laurence Cooper in collaboration with Drs. William Wierda, EJ Shpall, Chitra Hosing at MD Anderson Cancer Center, and Tom Kipps at University of California, San Diego (UCSD), are developing a CAR to recognize and respond to the ROR1 protein, which is relatively unique to CLL. There are also several other medical research centers around the country exploring variations of CARs.

A number of years ago, Drs. Kipps and Wierda discovered the ROR1 molecule on CLL cells while conducting gene therapy studies. ROR1 is a protein which is normally expressed on cells before birth but is switched off at approximately the time of birth. Because of its exclusive expression on the surface of CLL cells, ROR1 is a reasonably specific target for immune therapy. Subsequently, Drs. Kipps and Wierda have collaborated with Dr. Cooper and the other investigators at MD Anderson mentioned above to initiate a clinical trial to test the ROR1-specific CAR *(see interview with Dr. Cooper on page 3)*.

Current, effective therapies are not without risk. Therefore it would be a major advance if the immune system could be educated to be more proficient in killing CLL cells and prevent recurrence. Patients have been waiting for a specific therapy which does not damage the rest of the body for as long as cancer has been treated. CARs may or may not be the Holy Grail in eliminating CLL, but they most certainly will be part of the answer. : :

Driving CARs

TO THE FOREFRONT OF THERAPY

Dr. Laurence Cooper is Chief of Pediatric Cell Therapy at MD Anderson Cancer Center. In addition to caring for young patients undergoing hematopoietic stem-cell transplantation, he supervises a laboratory that develops and implements new immune-based therapies. He and his collaborators have combined gene therapy and immunology to adapt T-cells to target cancerous cells. Clinical trials infusing these T-cells are now under development.

HOW WAS THE POWER OF T-CELLS DISCOVERED?

Hematopoietic stem-cell transplantation (HSCT, formerly referred to as bone marrow transplantation) uses stem cells from either a matched donor or from a patient's own cells. What we have observed from stem cell transplantation is that donor-derived T-cells are able to sniff out friend from foe in the transplant recipient and are capable of killing off remaining malignant cells.

We therefore asked, "What can we learn from HSCT going forward to avoid the problems of toxicities, costs, etc.?" One answer is to give just the T-cells and strip away everything else. To do this, we have learned how to trick the T-cells and engineer them to have targeted specificity to only recognize malignant cells.

HOW DO YOU TRICK THE T-CELLS?

We insert chimeric antigen receptors (CARs) to tell the T-cells what to target. CARs are similar to antibodies. Antibodies have one end that binds to a molecule (antigen) on the malignant cells. The other end of the antibody recruits immune cells that eliminate the malignant cells. However, these antibodies have to interact with the patient's immune system which is compromised by their disease and/or chemotherapy, especially in patients with CLL.

What we are doing now has been decades in the making. Dr. Zelig Eshhar from the Weizmann Institute in Israel discovered that just the antigen binding domain of an antibody, what we call the CAR, can be stitched onto the surface of a T-cell. The external portion of the CAR is on the lookout for antigens. The attached portion of the CAR causes the T-cell to proliferate, to make cytokines which contribute to an inflammatory response, and importantly to kill. Infusion of the T-cells genetically modified to express a CAR provides the patient with everything they need: the power of antibodies to detect malignant cells with the ability of T-cells to eliminate malignant cells.

Over the years we have improved upon the CAR design to fully activate a T-cell and to take on all of the T-cell properties. We are currently using CARs to target CD19 and ROR1. One trial using a CD19-specific CAR for patients with B-cell malignancies is actively accruing at MD Anderson.

WHY WERE CD19 AND ROR1 CHOSEN TO BE TARGETED?

CD19 is a protein expressed on B-cells, which are cells in the immune system that make antibodies. CLL is a disease arising from malignant B-cells. For the first trial, T-cells will be taken from the patient prior to HSCT and genetically modified to introduce the CD19-specific CAR. Patients will undergo an autologous HSCT (meaning they receive their own stem cells) and then receive their modified T-cells.

So patients get a bonus. As they receive the HSCT, they also benefit from the CD19-specific T-cells trying to eradicate their disease.

The ROR1-specific CAR is in collaboration with Dr. Tom Kipps at UCSD and Dr. Bill Wierda at MD Anderson. In Dr. Kipps' lab an observation was made that ROR1 is expressed only on the malignant B-cells of CLL. We hope that by making a CAR specific to ROR1 that the specificity is redirected to just the malignant B-cells, unlike the CD19-specific CAR which targets both healthy and malignant B-cells.

WHEN WILL ROR1 EXPRESSING CARS BE TESTED IN PATIENTS?

We are gearing up right now to put the trial through the regulatory process with Dr. Wierda and Dr. Kipps. We know that the CAR works, we know how to get the CAR into T-cells and we know how to maneuver through the regulatory pipeline. We are still working on the manufacturing procedures to grow ROR1-specific T-cells in high enough numbers so that they are effective when given back to the patient. This is a solvable problem, but it is going to take some more work. I expect that we will submit the trial for approval in the fall with hopes of opening early next year. Initially the trial will only be open at MD Anderson, and then we anticipate opening the trial on the West coast to accommodate the needs of Dr. Kipps' patients.

FAQS

Dr. William Wierda, Associate Professor of Medicine in the Department of Leukemia at MD Anderson, is actively exploring immune therapy approaches for CLL. Below he provides answers to some common questions about CARs.

ARE THERE SPECIFIC CONCERNS YOU WILL BE WATCHING FOR IN THE CLINICAL TRIALS?

A trial using a CD19-specific CAR is currently being conducted by Dr. Carl June at the University of Pennsylvania for B-cell malignancies. One of the observations from his trial is that patients with CLL benefited from the T-cell infusion! *(Note: these results were widely reported in the media.)* However, the healthy B-cells of patients disappear after this therapy as CD19 is expressed on both malignant cells and normal B-cells. You can live without B-cells for a certain amount of time because we can replenish antibodies with intravenous immunoglobulin (IVIG) therapy. Nonetheless it would be better for the patients if we could just restrict the killing to the malignant B-cells, and this is why the ROR1-specific CAR is worth testing.

> "The hope is that one day… patients can eliminate their disease with just an injection of T-cells."

Also, the CAR-modified T-cells are quite potent. When infused into the patient, these T-cells disseminate throughout the body and when they bind to CD19 they can simultaneously become activated. Patients consequently can experience side effects such as fever and shakes. The ability to manage these types of infusion-related toxicities is important. Fortunately, we are able to learn from Carl's [Dr. June's] experiences and adapt our trials accordingly.

IS THERE POSITIVE DATA FROM ANY OF THE CAR TRIALS WHICH HAVE BEEN CONDUCTED?

There is a lot. Trials infusing CAR-modified T-cells are taking place all over the world for various disorders. There is one published case report from the NCI, and Dr. June has promising preliminary data from his trial using CD19-specific T-cells.

IS THERE AN IDEAL PATIENT GROUP YOUR RESEARCH WILL BENEFIT?

Initially these trials are only open to patients with aggressive diseases refractory to other treatments or at high risk for relapse. If everything goes well, the goal is for all CLL patients to benefit from T-cell therapy. The hope is that one day this approach can replace HSCT and even chemotherapy, so patients can eliminate their disease with just an injection of T-cells.

AS A PEDIATRIC PHYSICIAN, WHAT IS YOUR INTEREST IN STUDYING CLL, WHICH IS CONSIDERED AN "ELDERLY DISEASE"?

I have witnessed the power of T-cell therapy and one of the more compelling areas to try it is the field of CLL. These patients are burdened by this chronic illness and often cannot receive a HSCT for one reason or another; they are too old or too sick. With the ability to harness a patient's T-cells and redirect the specificity, we are now capable of creating a targeted therapy that can benefit CLL patients today and can be applied to treat diseases of malignant B-cells in children tomorrow.

WHAT IS YOUR MOTIVATING FACTOR TO CONTINUE RESEARCHING?

The belief that I can make a difference is what keeps me going. I know I can help patients if I innovate and work hard. : :

WHEN WILL CARS BE WIDELY AVAILABLE TO ALL PATIENTS?

Significant work is still needed on CAR research and clinical application before this becomes a treatment that can be generally applied to patients. When we know it is safe and know how best to give it to patients, it will become generally available. Because it involves taking the patients' own T-cells and modifying them to express the CAR gene, patients' cells must be manipulated in highly specialized laboratory facilities. The logistics and implementation of this is very different from a pill or IV medication that can be dispensed by a pharmacy.

WHEN WILL CARS RECEIVE FDA APPROVAL?

It will probably take several years of clinical testing. Many variables go into FDA approval: pharmaceutical companies have objectives and agendas; feasibility can be an issue; and short and longer term safety must be assessed; etc. CARs are a highly specialized treatment which must be done at a specialized center. Experimental therapies - and this is very experimental therapy - do not usually get special treatment from the FDA just because they look promising or make big headlines.

HOW DO I FIND OPEN CAR TRIALS?

There are several groups around the country studying CARs. There is limited published information thus far, indicating that this is early in clinical development. Currently, the best way to determine if there are open clinical trials testing CARs is to search via www.clinicaltrials.gov. For clinical trials, most patients will probably have to be previously treated or refractory to standard treatments before they are eligible. : :

THE DOMINO EFFECT:
Btk's Role

The human body is full of cells, genes, proteins and other molecules working together to keep people alive and healthy. Much like a relay race or dominoes, the action of one molecule activates another molecule which activates another molecule and so on. These chains of activation are called pathways and occur through the use of signals.

Bruton's tyrosine kinase (Btk) is an enzyme (a type of protein) expressed in B-cells, including CLL cells, and has significant implications in their survival. Below Dr. Jan Burger (MD Anderson Cancer Center) has provided information on Btk and how researchers are targeting the enzyme to eliminate CLL.

HISTORY OF BTK

The Btk enzyme is named after Colonel Ogden Bruton (1908 to 2003). He was a pediatrician at the Walter Reed Army Hospital and described the first case of X-chromosome linked agamma-globulinemia (XLA) in 1952. XLA patients lack circulating B-cells and have profoundly reduced immunoglobulin levels.

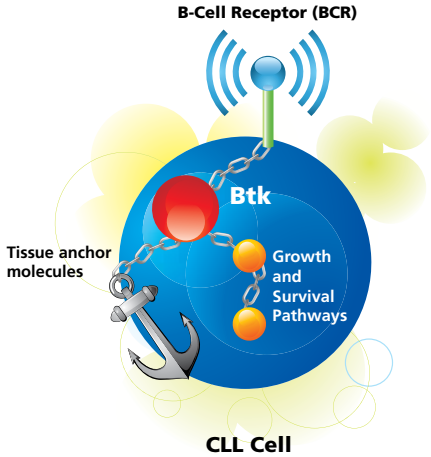
The genetic basis for XLA was discovered about 4 decades later in 1993. It was found that mutations in the Btk gene located on the long arm of the X chromosome are responsible for the disease. Because mutations of the Btk gene (which codes for the Btk enzyme) lead to such profound B-cell defects, Btk became an attractive target for B-cell malignancies. After studying Btk's function and structure, selective Btk inhibitors were developed, primarily for treatment of B-cell malignancies, such as CLL, and for autoimmune diseases.

HOW BTK WORKS

The Btk enzyme is a master regulator of B-cell function. It transmits signals received from surface receptors including the B-cell antigen Receptor (BCR). CLL cells receive signals for growth and survival through the BCR. Once the BCR is activated by these signals, Btk moves to the cell membrane and becomes activated. The activated Btk then stimulates the survival and cell growth machinery in CLL cells.

The BCR receives signals from outside of the cell and activates Btk. Activated Btk stimulates growth and survival in the CLL cell. Btk also helps anchor molecules work, which retain CLL cells in the lymph nodes. (Image 1)

The Btk inhibitor PCI-32765 binds to and inactivates Btk. As a consequence, CLL cell growth and survival is inhibited. Also, the anchor molecules no longer work, and CLL cells are flushed out into the blood, where they slowly starve and are more susceptible to treatment. (Image 2)



CLL Cell

(Image 1)

CLL Cell Treated with Btk Inhibitor

(Image 2)

In addition, our research has shown that Btk is involved in the migration of CLL cells from tissue to the blood stream by regulating surface receptors called chemokine receptors. Chemokine receptors function as anchors that tether CLL cells to the lymph nodes and the bone marrow. Once inactivated, CLL cells become anchorless and are flushed out of the tissues into the blood.

TARGETING BTK

The Btk inhibitor, PCI-32765, is currently being used in Phase I trials in CLL patients. During the first weeks of therapy, CLL patients treated with PCI-32765 experience rapid size reduction and normalization in lymph nodes, and at the same time develop lymphocytosis (an elevated white blood cell count). Inhibiting the dual activity of Btk - its effects on survival and cell growth on the one hand, and anchor signals that retain CLL cells in the tissues on the other - explains this clinical activity.

Once in the blood, CLL cells are deprived of their nutritious environment provided by the lymph nodes and slowly starve. This starvation is amplified by the blockade of the BCR, which is hindered by PCI-32765. After weeks or sometimes months of treatment, this starvation process takes its toll on the CLL cells in the blood, and lymphocyte counts trend downward. At the same time, normal blood cell counts (red blood cells, platelets, neutrophils) improve and patients achieve remissions.

WHITE CELL COUNT SIDE EFFECTS

One of the most remarkable activities of PCI-32765 is the rapid reduction in lymph node sizes, accompanied by very substantial, transient increases in blood lymphocyte counts, especially during the first few weeks of therapy. This re-distribution phenomenon of leukemia cells, moving from the tissues into the blood, is accompanied by remarkable improvements in sinus congestion, appetite, fatigue and energy levels along with normalization of blood levels.

continue on page 6

WHERE THERE IS A WILL, there is a way

Will Newman is a high school honor student from Asheville, North Carolina and a musical phenomenon. He has been playing music since the age of five. His musical ventures trump most, even though he has not yet graduated from high school. He opened for the Blues Brothers when he was ten years old and won the gold medal at the 2011 New York Wind Festival at Carnegie Hall with his high school symphonic band.

Will also has a personal connection to CLL and is committed to advancing CLL research. As an eleven-year old, he accompanied his father, Steve, to MD Anderson Cancer Center for his father's CLL treatment. "I learned that there were doctors and researchers around the world working tirelessly to find a cure. I wished that there was something I could do," Will stated.

Will has found a way to join the effort to support CLL research. He spent the first half of 2011 recording a holiday album entitled "Believe Again". The album includes five of Will's arrangements of traditional Christmas songs plus an original song called "Believe Again". Will composed the music and his father wrote the lyrics. Will plans for all proceeds from CD sales to be donated to CLL Global.

"I hope the money we raise by selling this recording will help bring us a little closer to the miracle we've been praying for," Will adds.

Individuals in the music industry are supporting Will's effort. Stephanie Morgan of the indie group *Stephaniesĭd* donated backup vocals for the album. One of Will's musical mentors, Tony D, produced the album. A music video with footage from the recording sessions is also included. The album can be purchased in CD format or online. You can contact Will via his website (www.willnewmanmusic.com) for a CD or follow one of the links on his website to download the album.

It is never too early to start thinking about holiday shopping. Holiday albums make great gifts and stocking stuffers, and you can have the satisfaction of knowing your money is benefiting CLL Global and Will's music career. If you or someone you know is planning a fundraiser or hosting an event, especially around the holidays, Will can perform and promote the album. His parents have not only donated all costs associated with the album, but have also graciously offered to support this cause and facilitate his touring efforts. Will's music is even better in person.

Email info@cllglobal.org for more information or contact Will directly via his webpage: willnewmanmusic.com. : :

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- Find out creative ways you can help solve the CLL research puzzle
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continued from page 5 (Btk's Role)

To date, we have not seen adverse effects from the elevated white blood counts during early treatment with PCI-32765. Therefore, there is not a need to act upon these transient increases. However, because it is desirable to accelerate the time to remission, we have designed a study in which continuous PCI-32765 treatment is combined with the rituximab antibody, given during the first weeks of therapy. This approach is expected to eliminate the lymphocytosis, as the circulating CLL cells will be cleared by rituximab.

BTK ANTAGONISTS IDENTIFY PATIENTS IN COMPLETE REMISSION

The current assessment for residual disease has limited sensitivity and does not account for CLL cells hiding in tissue such as the lymph nodes. Because of these limitations, patients who technically are in "complete remission" still have undetected dormant CLL cells. This is why CLL patients in complete remission typically relapse years after a successful standard therapy.

Mobilization and targeting of these dormant CLL cells could help eradicate residual disease, thereby getting us closer to our ultimate goal, to cure CLL. The Btk inhibitor PCI-32765 or other related drugs, such as CAL-101, would be ideally suited for this task because they do not appear to cause toxicities.

COMPLICATIONS OF INHIBITING BTK

At this time, we do not know the long-term consequences of Btk inhibition in patients with CLL. So far, the vast majority of CLL patients treated with the Btk inhibitor PCI-32765 are continuing their daily treatment, many for over one year. Most tolerate this drug very well and have not experienced any unexpected or cumulative toxicities. However, over time, Btk inhibition could result in reduced production of immunoglobulins with increased susceptibility for infections. Careful monitoring of immuno-globulin levels and substitution with IVIG when necessary will help in assessing and managing this potential risk.

The efficacy of immunizations and vaccinations in patients receiving therapy with a Btk inhibitor is currently unknown. Also, Btk may be involved in cell functions other than what has been described above. Continuous, careful clinical monitoring and awareness of potential risks related to infections and immunoglobulin levels are basic requirements as we move forward. : :