For CLL patients needing treatment, the options continue to improve. Monoclonal antibodies and other oral agents such as lenalidomide and the kinase inhibitors CAL-101 and ibrutinib (formerly known as PCI-32765) are proving effective in eliminating evidence of CLL cells in the body. Unlike common chemotherapy, these oral agents do not damage DNA and should reduce the risk of causing other cancers. Most of these therapies are currently only available through clinical trials. In addition, there are more therapies on the horizon that we expect will have a major impact.

When patients are told they have chronic lymphocytic leukemia (CLL), a disease they have probably never heard of, the word that often resonates with them is LEUKEMIA. This ‘L’ word strikes fear because of associations people make from seeing patients on television or watching dramatic movies where one of the characters has leukemia and is portrayed as being bald and requiring intensive chemotherapy.

The word that needs to be emphasized in chronic lymphocytic leukemia is not the ‘L’ word, but the ‘C’ word: chronic. The term chronic implies a slow moving form of disease. Having any form of leukemia is challenging, and I do not want to undercut the suffering experienced by some CLL patients.

But I am an optimist, and I have found an upside to having CLL versus an acute leukemia or another type of cancer. CLL patients have time; time to come to terms with the news, time to gather information on the disease and time to research the most up-to-date treatments.

It is important for anyone diagnosed with CLL to evaluate the options available to them. Patients should never be rushed into treatment decisions. Those patients who are in need of treatment in the short term should take a few days to weigh all options after speaking with their doctor. Only half of the patients who are referred to large research institutions will need treatment in the first four to five years. A quarter of patients will not need any treatment 10 to 15 years from diagnosis, and some may never require therapy for their CLL. The point is there is NO RUSH.

“The word that needs to be emphasized… is not the L word, but the C word: Chronic.”

With existing standard treatments for CLL, approximately 40% of patients show no sign of disease at 10 years after treatment. This is a significant improvement from the statistics a decade ago. A decade from now the statistics will show even more progress. I know this because of the availability of new and developing technology, the preliminary results of the promising new drugs mentioned above and because we are starting to grasp the who and what of the other 60% of patients.

continue on page 4
CLL is notorious for causing immune dysfunction. This leads to infections which in some cases can become severe. The impaired immunity is caused, in part, by faulty interactions between CLL cells and normal cells of the immune system, particularly T-cells. In a healthy individual, T-cells and B-cells collaborate to ensure the body is free from foreign invaders like viruses, fungi, bacteria and cancer. Studies demonstrate that CLL cells, which are malignant B-cells, prevent T-cells from properly functioning.

Chemotherapy further compromises immunity by depleting immune cells, thereby leaving patients more susceptible to infection. However, chemotherapy is a key component in treating cancer. Researchers have been working for several years to overcome the immune obstacles related to CLL. Emerging therapies are proving to be effective, not only in eliminating CLL cells, but also in reversing the immune dysfunction associated with CLL.

Lenalidomide is an oral drug used to treat B-cell and bone marrow malignancies, including CLL. It seems to reverse some of the defects in T-cells and the immune system in CLL patients. There are mild side effects (including low neutrophil count, fatigue, rash and intestinal complaints), but lenalidomide is generally well-tolerated. This makes it especially appealing for elderly patients who are often more susceptible to immune and therapy-related complications. The effectiveness of lenalidomide as a single agent for CLL is positive but not outstanding. Clinical trials are now testing lenalidomide combined with monoclonal antibodies such as rituximab and ofatumumab.

Teaching T-cells to attack malignant cells has long been considered the “holy grail” of immune therapy for cancer. Chimeric antigen receptors (CARs) may be the solution for which researchers have been looking. CARs are engineered receptors that are genetically inserted in T-cells and then expressed on their surface. They enable these T-cells to seek out a specific molecule and stimulate the T-cells to attack and kill the cell expressing the target molecule.

CARs engineered to target CD19, a molecule expressed on CLL cells and some lymphomas, are currently being tested in clinical trials. CLL Global is providing funding to Dr. Renier Brentjens (Memorial Sloan-Kettering Cancer Center) for a phase I clinical trial using a CAR targeting CD19. Preclinical work needed to open a clinical trial to test a CAR targeting ROR1 is currently in progress. Drs. Laurence Cooper and William Wierda (UT MD Anderson Cancer Center) and Tom Kipps (University of California, San Diego) receive funding from CLL Global toward ROR1-targeted CAR research.

Lenalidomide and CARs offer a glimpse into a new era of immunotherapy which holds promise for the future of CLL therapy. Years of persistence and dedication from CLL researchers and patients willing to try unproven treatments are starting to emerge in the form of new therapeutic options. While a significant amount of testing and information is still needed, researchers are optimistic that immunotherapy can become a standard treatment option, and the notion of a CLL patient with a normal immune system can become a reality.

MAPPING MUTATIONS

moving genetics forward

Knowledge of CLL genetics continues to increase exponentially due to new technologies. Dr. Stephan Stilgenbauer (University of Ulm, Germany) is well known for his expertise in CLL genetics. For his CLL Global Alliance project, he and his colleagues are performing whole genome sequencing of CLL cells.

Whole genome sequencing provides raw data on all six billion nucleotides in an individual’s DNA. (Nucleotides are the building blocks of DNA.) Deletions or abnormalities in the genetic code (the sequence of the nucleotides) contribute to the development of cancer and determine its clinical course. Cells are exposed to external and toxic stress, leading to mutations or “mistakes” that change the genetic code in the cell. While most of these mistakes will be silent or repaired, some of these mistakes alter critical genes, leading to a growth of cancer cells.

Modern gene sequencing technology holds the potential to provide unprecedented insights into the mutational signatures associated with different disease courses of CLL. While mutations located in key areas of certain chromosomes are known, a precise map of mutations of the CLL genome is currently missing. Dr. Stilgenbauer hopes to draft a map of mutations to answer key clinical questions necessary to move CLL research forward. Below is an interview with Dr. Stilgenbauer discussing the evolution of the field of genetics and work related to his CLL Global Alliance project.

WHY IS GENETICS SO IMPORTANT FOR RESEARCH?

Genetics is important for research because the genome of the cell is the primary determinant of its behavior. Changes to the genome, particularly changes that translate through RNA and proteins, lead to disease and also affect the outcome of patients. Understanding genetics is one of the most important aspects in curing any disease.

WHY DID YOU GET INTO CLL RESEARCH?

It was a mixture of mostly good luck and a bit of dedication. I started working with Peter Lichter and Hartmut Döhner, two very important genetics and CLL scientists, just at the onset of their careers. There was limited information at the time regarding CLL genetics, but technical developments such as FISH, CGH, and DNA sequencing allowed the field to develop very rapidly. Also, when I started attending meetings such as iwCLL, I got to know the CLL authorities like Kanti Rai, Jacques-Louis Binet, Guillaume Dighiero, Daniel Catovsky, Emili Monserrat, and Michael Keating. To me these individuals are not only exceptional doctors and researchers, but most importantly they are very nice people. It was simply an inviting atmosphere and a good spirit of collaboration. They were inspiring each other. That supported my choice very much.

WHAT WAS KNOWN ABOUT BIOLOGY AND GENETICS IN CLL WHEN YOU FIRST BECAME A RESEARCHER?

When I entered CLL research, it was still considered a relatively “boring” disease. There were not many treatment options and the biology looked like a disease of relatively normal lymphocytes that just float around and do not do much harm. Over the years it has been recognized that there are subgroups of CLL, and most importantly that certain molecular and biological findings are very closely linked to the rate of disease progression and the survival time of patients. These subgroups have become very important with regard to prognosis, and obviously we have had a dramatic development with regard to the treatment. We have opportunities not only to find out something about biology but to also use that biology to direct our therapy.

WHAT ASPECT OF CLL RESEARCH IS SHOWING THE MOST PROMISE AT THE MOMENT?

The new genome sequencing approaches will certainly bring about the next genetic revolution by identifying multiple abnormalities associated with the clinical behavior of the disease. This will allow us, not only to predict how the disease will behave, but also to direct treatments to specific groups of patients. We are dramatically and continuously improving on the understanding of disease biology with more targeted therapies. The link between biology and treatment is already benefiting disease understanding and also the treatment of patients. Agents that focus on specific aspects of CLL biology such as the inhibitors of B-cell receptor signaling and apoptosis regulators clearly hold the greatest promise to bring the next revolution in CLL therapy, driven by biological disease understanding.

HOW IS WHOLE GENOME SEQUENCING PERFORMED?

Blood samples are taken from patients, and the CLL cells are separated out. The chromosomes of a cell are unraveled, and the entire content of the DNA is examined. Sophisticated technology determines the nucleotide sequence of every gene. To analyze and understand which genes are mutated, we are sequencing both CLL cells and normal, healthy cells of patients. We then look intra-individually at what changes are present in the tumor DNA compared to the normal cells to determine mutations. This technique will be performed in several patients, comparing different disease courses and responses to various treatments. There will be a significant amount of data to analyze and to compare to establish which genetic mutations are related to CLL.
We now know that there are several subgroups of patients and we recognize the subgroups where more research should be focused. Most current treatment statistics pertain to patients younger than 65 years of age. In reality more than 50% of patients are diagnosed when they are over 70 years of age, and unfortunately it is less clear how older patients tolerate and respond to therapies. Emphasis is now being placed on understanding CLL in this large subgroup of patients. Clinical trials specific to patients 65 and older are now underway.

Florescence In Situ Hybridization (FISH) gave researchers a new understanding of CLL in the early 2000’s. This test has helped identify subgroups of patients that have a greater need for more research and new therapies. Technological advancements will give us the opportunity to really understand the biology and genetics of this disease and treat individual patients accordingly. CLL Global is currently funding several projects using these new technologies. Further details of some of these projects are on page 5.

Questions patients frequently ask when first diagnosed include, “What should I do about diet and alcohol intake?” or “What should I do about my life?” My recommendation is to focus attention on the important issues such as family and general health. Find things that bring true joy, and keep on doing those things. Many patients say that a diagnosis of slow moving CLL has given them an opportunity to reevaluate what is most important to them. When we finally cure this “bloody” disease, we are going to change the ‘C’ in CLL into an ‘L’, so that all patients are diagnosed with Living Life Large.

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.

IS WHOLE GENOME SEQUENCING BETTER FOR CLL RESEARCH THAN OTHER TECHNOLOGIES LIKE FISH?

We hope so, and initial evidence is supporting this. With FISH we know that we are detecting important abnormalities, but we detect only what we look for. With these new approaches we can identify new abnormalities that we cannot detect with FISH. The best approach is not to focus on the genes that we know of, but to take an unbiased approach toward looking at all genomic regions.

HOW IS RESEARCH IN GERMANY BENEFITTING ALL CLL PATIENTS?

We have the habit of being structured and organized. The German CLL Study Group offers a very dedicated structure of setting up clinical trials which are basically open to all sites, not only in Germany, but in other countries as well. What to me has always been very important in running strong, quality science projects is bio-banking [the storing of human biological samples for research purposes] within the clinical trials. This allows easy analysis of biological factors of patients. For example, once we have established a list of abnormalities from gene sequencing, we can use banked samples to verify our work. Or we can validate correlations between certain mutations and patients’ response to treatment. This benefits all patients. We must go both ways for our patients: from bench to bedside and from bedside to bench.

WHAT MAJOR CHANGES WILL COME IN CLL IN THE NEXT FEW YEARS?

I think the coming years will be full of dramatic developments with regard to biology and treatment. The increasing spectrum of biologically directed therapies will really be the way forward and hopefully one day make classical chemotherapy much less frequently used or even obsolete. Chemotherapy currently is the backbone of our treatment. However, our hope is that within a couple of years at least some patient subgroups get away from chemotherapy and strong candidates are patients with TP53 mutations, patients who do not tolerate chemotherapy or patients with comorbidities.

Many of us believe that new immunological approaches offer tremendous potential. Modified T-cells such as the CAR [chimeric antigen receptor] technology hold great promise; clinical agents such as lenalidomide are very useful drugs through their actions on the immune system; and last but not least, monoclonal antibodies have already changed the treatment of CLL and will continue to do so in the future with the development of new antibodies.

DNA is packaged in chromosomes. There are 46 chromosomes (23 pairs) in almost every cell in the body. DNA is made up of nucleotides, which are represented by the letters A, C, G and T. Each “rung” on the DNA ladder contains two nucleotides. Scientists are looking at every nucleotide in CLL cells to find all abnormalities and deletions.

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MEET THE LATEST
grant recipients

Dr. Xavier Badoux (University of Sydney, Royal North Shore Campus, Australia) is focused on better understanding the relationship between treatment with the fludarabine, cyclophosphamide, rituximab (FCR) regimen and specific prognostic factors in the elderly CLL population. Most data regarding FCR and the TP53 and ATM genes (these genes are found to be abnormal or deleted in some CLL patients) are derived from clinical trials where patients are younger than the average age of CLL patients (72 years). With funding from CLL Global, Dr. Badoux will use next generation sequencing technology to analyze the TP53 and ATM genes in-depth. Given the overwhelming evidence linking mutations in these genes with clinical outcomes, sequencing these genes will provide clinically useful information. A panel of additional targets hypothesized to be involved in CLL will also be tested.

Deletions of chromosome 13, specifically the 13q14 region, are the most common genomic alterations in CLL. It was previously reported that two small molecules, miR-15 and miR-16, are located in this deleted region. Furthermore, miR-15/16 are reduced in expression in most CLL cases, and the loss of these two small molecules plays an important role in the initiation of CLL. Dr. Yuri Pekarsky (Ohio State University) and his colleagues are investigating the DLEU7 gene which is located in the deleted region of chromosome 13q. They hypothesize that DLEU7 may cooperate with miR15/16 in the initiation of CLL. Dr. Pekarsky will clarify at the molecular level how inactivation of DLEU7 contributes to CLL and establish whether DLEU7 can be used as a target for developing therapeutic approaches for CLL.

Between 2009 and 2011, Dr. Carmen Schweighofer (University of Cologne, Germany) studied at UT MD Anderson Cancer Center under Dr. Lynne Abruzzo, a clinical cytotgeneticist and member of the CLL Global Alliance. Drs. Schweighofer and Abruzzo discovered gene-signatures in the DNA of CLL cells which may predict time-to-treatment and overall survival in previously untreated patients. Tests were conducted in peripheral blood samples from CLL patients at MD Anderson. Specifically, looking at expression levels of only two genes, and up to 13 genes, allowed them to identify specific subgroups of patients. Dr. Schweighofer has recently returned to Germany where she will validate these gene signatures in an independent cohort of patients.

Translational research is important in understanding CLL and its connection to clinical applications. One of the burning questions scientists are beginning to answer is why CLL cells do not die as normal cells do. One of the reasons is because the CLL cells express high levels of proteins that inhibit programmed cell death, or apoptosis. Dr. Kumudah Balakrishnan (UT MD Anderson Cancer Center) and her colleagues have identified a specific protein called SMAC/DIABLO which normally aids in implementing apoptosis in cells, but does not function properly in CLL cells. For her CLL Global project, Dr. Balakrishnan will mimic this protein in CLL cells. Her laboratory studies will provide a better understanding of the balance between the pro-survival and pro-death pathways and should also provide knowledge critical for optimizing targeted therapies.

This year four researchers whose projects show the most promise in meeting the goals of CLL Global were selected. All of these recipients are up-and-comers in the CLL research community who have worked with some of the best CLL researchers in the world.
TAKE MATTERS into your hands

It is no secret that CLL is an orphan disease which means it affects a small population. The consequence to this is inadequate funding from the medical industry and little attention from the population as a whole. The bottom line is that CLL patients have to put their fate in their own hands.

CLL Global has been providing a bridge for individuals who are willing to contribute to the researchers in need of funding. The Foundation is well recognized in the CLL research community for fulfilling a much needed gap. While CLL Global continues to grow and to have a larger impact, the momentum in the CLL research community is simultaneously progressing faster than ever before. Ground breaking ideas (i.e. CARs, page 2) and better technology (i.e. whole genome sequencing, pages 3-4) have the CLL community enthusiastic for the future.

Continuous funding is needed to keep these projects going. There are additional, promising research endeavors in need of support. While not every person can or wants to write a check to contribute, it does not mean you cannot be a part of the solution. Since day one, many individuals have utilized their skills and talent to encourage others in their network to contribute to CLL Global. Supporters have also been generous to host events. These are great donation generators, and CLL Global is appreciative of the work involved in organizing these functions. The Foundation is fortunate to be able to rely on individuals to take on this task, as this allows for staff time to go toward managing the research program.

CLL Global is a small but vibrant and vital organization. Each of our supporters can play an important role. We need you to take action to fund outstanding research like the projects discussed in this issue of the Momentum. We are happy to provide materials such as newsletters and brochures for you to spread the word.

POTENTIAL OPTIONS

- Letter writing campaign
- Family cookbook
- Golf tournament
- Ask kids and grandkids to help fundraise
- Presentations to schools and communities
- Run / walk
- Utilize your creative talents
- Leave CLL Global brochures at your doctor’s office

We are happy to provide materials such as newsletters and brochures for you to spread the word.

UTILIZE THE WEB

Use GoodSearch (powered by Yahoo!) to surf the web. CLL Global gets a penny for every search.

GoodShop has partnered with thousands of online stores. A percentage of a purchase made online can be donated to CLL Global.

Eat at participating GoodDining restaurants and a donation will be made to CLL Global at no additional cost to you every time you eat out.

Create a grassroots community on Causes on Facebook or join our Cause to support CLL Global, spread awareness and take action.

Make a Wish via Causes on Facebook to host your own fundraising campaign to benefit CLL Global. Wish options: birthday, wedding, run/walk/ride, holiday, memorial, and personal wish.

List items on eBay and a percentage of the sale can be donated to CLL Global through MissionFish.

GO TO WWW.CLLGLOBAL.ORG TO:

- Sign up for Tidbits, our monthly e-newsletter
- Watch videos from CLL Global grant recipients
- Search for specific topics related to CLL
- Read commentary from the CEO of CLL Global, Dr. Michael Keating
- Learn more about projects we are accelerating
- Follow us on Facebook