Moving CLL Research Forward – A Progress Update

A GLOBAL QUEST
for progress

Cll Global believes that finding the cure for CLL will be much like completing a jigsaw puzzle. If a researcher only focuses on his or her section of the puzzle, pieces will be absent or unnecessarily duplicated. Ideas, clues and discoveries from researchers at other institutions and countries will be missing. As you are aware, the US/European Alliance was established to include investigators from a number of countries in Europe to interface directly with US investigators. A lesser known fact is that we have played a seminal role in developing research groups in non-European countries, namely Australia and Israel. This truly enhances our global reach.

In March, I had the privilege of hearing presentations by individuals who have received funding from the CLL Australian Research Consortium (CLLARC). CLL Global provided the seed funding to establish CLLARC. It was refreshing to listen to the energy that these investigators are putting into their research.

Dr. Stephen Fuller (University of Sydney) and colleagues have rigorously investigated the genetics of families with a very high incidence of CLL through multiple generations. The researchers have investigated millions of sequences from these families and have identified at least two potential genetic areas that might increase the risk of developing CLL. The most promising is an area on chromosome 14q which is highly active in the development of the lymphoid system. Within this region, a gene currently identified as “mutant gene X” appears to be strongly associated with familial CLL. Collaborators in the global community will provide Dr. Fuller and his group with related cases to evaluate.

Research at MD Anderson Cancer Center has found a clustering of 14q abnormalities in association with the trisomy 12 abnormality. Will mutant gene X be involved in this connection? Further research is needed. The identification of a familial CLL gene may help us understand the high incidence of CLL in Ashkenazi Jews. This is an ongoing research priority for our Israeli group, the CLL Israel Research Consortium (CLLIRC).

Another area of interest is a protein called heatshock protein 90 (hsp 90). It is thought to be significant because of its relationship with ZAP70, an important prognostic factor in CLL. Previously, early-generation inhibitors of this protein were studied in clinical trials. The results indicated minimal activity with some toxicity. However, more recently other molecules have been evaluated. Dr. Giles Best (University of Sydney) and colleagues are working with an inhibitor called SNX7081. The initial findings indicate that the drug is effective against CLL cells. There appears to be a strong synergism between SNX7081 and fludarabine, particularly in patients with the most challenging abnormalities. With additional research, clinicians will be able to determine whether SNX7081, alone or in combination, will represent a new treatment strategy.

Dr. David Gottlieb (Westmead Millennium Institute) has been working in the transplant area and is convinced that the development of chimeric antigen receptors (CARs) against CLL is going to be important. CARs force immune cells to recognize and destroy CLL cells. His work to develop methods of reconstituting the immune system complements the work of the members of the US/European Alliance. Gottlieb’s work suggests that the CARs will be active against not only the CLL cells but also a number of viruses such as Cytomegalovirus and Herpes Zoster which causes shingles. These viruses are a frustrating complication of CLL treatment; clinicians and patients would welcome a reprieve of this side effect.

Long term collaborators Dr. Stephen Mulligan and Dr. Richard Christopherson (University of Sydney) have been looking at surface markers on CLL cells to triage patients with aggressive disease. They have also developed a concept of demibodies which only kill cells that express a particular pair of surface molecules (or antigens). Current therapeutic antibodies target a single antigen. With demibodies, it may be possible to selectively target cells co-expressing CD5 and CD20, the hallmark of CLL cells. This technology remains in pre-clinical development, but represents a promising opportunity.

It is obvious that a significant amount of research is occurring in Australia. I will be traveling to Israel soon and will give you an update of the progress made by the CLLIRC in a future Momentum. Meanwhile, we continue to search the globe for the necessary pieces to cure CLL. As our name indicates, this puzzle requires a global effort.

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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.
The most recent CLL Global US/European Alliance meeting, held in Houston in January, was a major success. A priority of the Alliance has always been to advance CLL science. Over the course of the last year, a new genetics group was introduced to improve our understanding of this cutting edge research. Modifications are also required from meeting to meeting in order to keep minds fresh and forward thinking. At this meeting, the theme was based on “Challenges and Opportunities.”

Patients with 17p deletions and p53 abnormalities are undoubtedly the most unmet need in the management of CLL. Stimulating presentations touched on the current understanding of the impact of mutations, the association with other genetic abnormalities and the evolution of this genetic change as the disease progresses. It is clear that new approaches are needed, free of chemotherapeutic agents that are relatively ineffective in this condition. Researchers are getting closer to changing the outcome of this group of patients by preparing them earlier for stem cell transplantation. A number of ideas percolated up, and there is no doubt that there will soon be p53 specific studies reported in the CLL research community. “Closing in on a Killer” on page 5 acknowledges the weaknesses in this group of patients, but also provides new answers.

Large cell lymphomas and the Hodgkin’s disease transformation of CLL, commonly known as Richter’s transformation, was another challenge topic for researchers. More interest is being paid to the role viruses play in causing transformations and to the development of immune therapies for this condition. Certain agents damage the immune system and the DNA of the CLL cells which may lead to these transformations. Ways to decrease patients’ exposure to these agents are under investigation.

The opportunity to target the B-cell receptor signaling pathway, an important communication mechanism for CLL cells, generated tremendous enthusiasm among attendees. This well known pathway received relatively little exploration until recently. Current interest was sparked by a better understanding of the CLL stroma/microenvironment (a network of supporting cells and molecules). Ongoing collaborations between the New Drug Development group and the CLL-Stromal Interaction group explore how these drugs, which target the B-cell receptor’s pathways, can be used most effectively.

Another idea which will be explored is CARs, or chimeric antigen receptors. These receptors turn a patient’s immune cells into cells capable of recognizing their own CLL and killing them. CARs will likely be most effective in patients with intact immune systems and residual disease. CAR studies in CLL are now well underway. The next few years will provide answers about the strengths and weaknesses of different CARs.

CLL researchers have identified challenging areas and have strategies in place. Going forward, many clinical trials will provide targeted approaches to accommodate specific subgroups of CLL patients. Knowledge gained from the therapeutic dissection of the disease will be applied to new strategies. In the near future, all CLL patients will have the opportunity to be provided with a successful, personalized plan. Stay tuned. The best is yet to come.

Learn more about the Alliance and watch interviews with Alliance members at http://www.cliglobal.org/CLLnews/multimedia.htm
MicroRNAs: BIG THINGS COME IN SMALL PACKAGES

MicroRNAs were first discovered in worms in 1993, and later in flies, mice and plants. MicroRNAs are very small genes. Genes are pieces of DNA. Many genes code for proteins, which in turn allow cells and the body to grow, heal and function. MicroRNAs do not code for proteins. They control the growth, death, shape and maturation of cells by serving as guardians over the genes coding for the proteins. If microRNAs see a glitch in the production, they will turn off the gene which is malfunctioning.

Until the last decade, microRNAs and other non-coding RNAs were considered “junk DNA” of the human genome. Because this portion of DNA does not code for proteins, it was assumed that it did not have a purpose. Also, genes which code for proteins are made up of approximately 2000 nucleotides (nucleotides are the building blocks of DNA and RNA). MicroRNAs are approximately 20 nucleotides. Their small size led scientists to believe that they were unimportant. However, once Drs. George Calin and Carlo Croce discovered that some of this “junk DNA” was linked to a common chromosomal abnormality in CLL (chromosome 13q-) a world of microRNA research exploded. Not only are microRNAs now considered to be very important, but the functions of other non-coding RNAs, also formerly classified as “junk DNA”, are now being explored.

Q & A with Dr. George Calin: MEET A GENETIC PIONEER

Whether it is destiny or just plain luck, life encounters with the right people in the right places at the right times can have a major impact on society. Dr. George Calin always had a natural interest in genetics and molecular biology. The paths he chose and decisions he made are impacting cancer research and science in general.

Dr. Calin acquired his MD and PhD in his native country of Romania. After graduating, he ventured to Italy to further study under Dr. Massimo Negrini, a well known geneticist. Once his apprenticeship was complete, he returned to Romania where he then specialized in gastroenterology and emergency medical care. His continued interest in genetics and a lack of resources in Romania brought him to America where he worked under Dr. Carlo Croce, first at Thomas Jefferson University, and then at Ohio State University. It was in Dr. Croce’s lab that Dr. Calin made a discovery that is changing the textbooks.

HOW DID YOU LEARN ABOUT GENETICS WHEN YOU WERE YOUNGER?

Growing up in Romania, genetics was seen as a secondary science. I learned by myself through the limited scientific literature available, and I had a very good teacher, Dr. Dragos Stefanescu, a scientist in a cytogenetics laboratory at the Carol Davila University in Bucharest.

“...decisions he made are impacting cancer research...”
WE UNDERSTAND YOU MADE A DEDICATED EFFORT TO LEARN ABOUT MOLECULAR GENETICS. WHAT WAS THE OUTCOME?

Between 1996 and 1997, I sent 120 letters to scientists around the world, including Carlo Croce in Philadelphia, stating something like, “I would like to learn, but I have no background.” I received about 10 answers, and it was because of these letters that I went to Italy. Massimo Negrini was working in Carlo Croce’s lab when my letter was received. He was returning to Italy where I had also written to his new boss. So Negrini discovered from two different places that there is a crazy guy who is sending letters. He ultimately invited me to work in his lab and gave me a chance.

DID YOU COME INTO CLL RESEARCH BECAUSE OF CYTOGENETICS?

Yes, CLL is a very good disease for researching cytogenetics because of the chromosomal abnormalities. This is a good point to make- that by chance Croce and I, we were both working with chromosomes in different locations, both of us realizing that cytogenetics is important. I went to work in his lab at the recommendation of Massimo Negrini, and this is when everything happened.

HOW DID YOU DISCOVER MICRORNAS?

It’s all luck. Had I not gone to Carlo Croce’s lab, I would not have made these discoveries. He gave me the “worst” project (newcomers always get the worst projects), which was cloning genes in CLL. They were trying to figure out the genes involved in the 13q- abnormality, but no real progress had been made for more than one decade before I arrived in his lab in 2000.

You must also understand that Croce was never telling us point-by-point what to do, but gave us the “liberty” to discover. There are laboratories where the PI [principle investigator] does not allow you to jump into other types of research. If I worked in a place like that, I would do what the PI was asking me and I never would have found microRNAs.

YOU STRAYED FROM THE PROJECT YOU WERE GIVEN?

Yes, because the project was not successful. We were trying to discover a new type of gene. This was the point. I started reading anything and everything. When I read about these new genes originally found in worms, then flies and mice, I decided to clone them in humans and this was it. It is important to know that normal genes are much larger than microRNAs, so no one was looking for something so small in humans, especially something responsible for cancer.

WERE OTHER RESEARCHERS SKEPTICAL OF THE IDEA OF MICRORNAS HAVING SIGNIFICANCE IN CANCER?

Yes, 99% of them. The belief at the time was that microRNAs are not important. Also, we used classic genetic approaches in good samples from patients while others were spending a lot of money performing high level experiments without success.

TEN YEARS AGO THERE WAS NO INFORMATION ABOUT MICRORNAs. TODAY THERE ARE COMPANIES DEDICATED SPECIFICALLY TO EXPLOITING MICRORNAS. WHAT IS IT LIKE TO KNOW YOU ARE RESPONSIBLE?

I know I have to do something different.

DO YOU THINK THAT MICRORNAs ARE GOING TO BE THE CURE FOR CANCER?

Yes, but it depends on the type of cancer you are working on because the genome has so many other genes. In CLL microRNAs are very important. By targeting miR-15 and miR-16 [the microRNAs discovered in 13q-] great advances can be made for patients therapeutically speaking. But, for example, in colon cancer where there are so many abnormalities and so many genes, microRNAs will probably not have an immediate, huge impact in therapy. I think they do have a huge impact in identifying biomarkers in all cancers.

ARE MIr-15 AND MIr-16 SIGNIFICANT IN ALL CLL PATIENTS?

I do not believe they are important in 100% of cases because CLL is a very diverse disease. We think these are the genes of indolent CLL. For the aggressive CLL, I do not know how important they are. This is why we now are trying to find the microRNAs and other non-coding RNAs associated with 6q- and 17p-.

WILL ANY OF THE PROJECTS YOU ARE WORKING ON NOW BE BENEFICIAL TO PATIENTS SOON?

We have a project on plasma microRNAs [recently funded by CLL Global] which I think will help us find biomarkers to predict a patient’s response to therapy. This can be applied universally in five years. Gene therapy is difficult because first you have to get approval, followed by laboratory experiments and phase I and phase II trials. This is a lot of work and the earliest this will be applicable is 5 to 10 years.

YOU HAVE YOUR MD, SO WHY HAVE YOU CHOSEN TO DEDICATE 100% TO RESEARCH?

I sometimes think about taking the exams needed to go back to seeing patients. I very much enjoyed working in emergency care. I also enjoy science because every day is different - we have projects to work on, manuscripts to write, grant applications to submit. I travel and give several talks and I interact with different people every day. If you make important discoveries it is difficult to leave research.

Read the complete interview with Dr. George Calin on our website, www.cllglobal.org under the News & Views section.
Treatment for patients with CLL has been dramatically improving in recent years. In particular, the introduction of FCR (fludarabine + cyclophosphamide + rituximab) was a breakthrough with regard to more effective therapy. A large proportion of CLL patients will achieve a complete remission and FCR almost doubles progression-free survival in comparison to classical chemotherapy. Most notably FCR is the first treatment that in historical and randomized comparisons was shown to significantly prolong overall survival for CLL patients. The great efficacy of FCR in the vast majority of CLL patients has also led to the observation that there are subgroups of patients who do not benefit as much from this treatment. One specific marker that helps to identify such patients is 17p deletion. This is due to the genetic material that is damaged or lost in their CLL cells. Located on chromosome 17 is an important tumor suppressor gene, TP53. This gene usually functions as a “master watchman” of the cell by deciding if damaged cells should be repaired or killed. The absence of this gene means that CLL cells will not be instructed to die, even those badly damaged by chemo or other therapy. Even more unfortunate, the damaged, mutated cells can reproduce.

Not all patients with the 17p deletion or TP53 mutation will need treatment. However, when treatment is required, evidence has shown that patients with 17p deletion generally do not respond as well to classical chemotherapy. Approximately half of all CLL patients who are refractory to FCR first-line treatment will have a TP53 abnormality. Therefore the testing for 17p deletion and TP53 mutation should be incorporated into the routine clinical work-up of patients before beginning treatment. Fortunately, there is evidence that newer treatment modalities may offer hope for the patient population with a 17p deletion or TP53 mutation.

Response rates show that the monoclonal antibody, alemtuzumab (Campath), shows efficacy irrespective of 17p deletion or TP53 mutation status. Nevertheless, the remission duration for patients with 17p deletion and TP53 mutation after alemtuzumab is still short, indicating the need for additional treatment. Current clinical trials aim at improving response rates to alemtuzumab by adding high dose corticosteroids. Consolidation treatment with allogeneic stem cell transplantation or maintenance therapy (e.g. with alemtuzumab or lenalidomide (Revlimid)) are expected to prolong survival for this subgroup of patients. It has been observed that 17p deletion or TP53 mutation do not influence the long-term outcome of CLL patients after allogeneic stem cell transplantation. Because these patients will most likely not respond well to current therapies, it is becoming more common to prepare these patients for transplant after a first round of treatment. Therefore, allogeneic stem cell transplantation is recommended in international guidelines for patients with 17p deletions or TP53 abnormalities. This shift in strategy, along with advances in technology, has improved the outcome. (see Transplant: No Longer Last Resort on this page).

Beyond these currently available treatment strategies, new developments are being explored, including a wide range of novel agents specifically targeting abnormalities of the CLL cells. There is evidence to suggest that these new agents may offer hope for treatment options with better efficacy and tolerability as compared to classical chemotherapy in CLL. Many of these agents are currently available in clinical trials at centers around the world and can be offered in particular to those patients who do not benefit as much as others from treatments such as FCR. Obviously, patients whose leukemia cells harbor 17p deletion or TP53 mutation are among the prime candidates who should be strongly considered for these clinical trials.

In the late 1990’s, the observation was made that low doses of therapy were sufficient to allow the engraftment of the donor cells. It was also noted that the donor immune system could completely replace a patient’s marrow function, and in the process, often cause remission of the underlying malignancy (CLL or lymphoma). This brought about a major shift in the use of transplant as a treatment, using a less toxic regimen and allowing the treatment of older patients or those with other medical problems.

Currently the regimen used in Seattle at Fred Hutchinson Cancer Research Center is outpatient treatment with fludarabine, rituximab and one fraction of total body irradiation followed by the infusion of donor cells. Many patients never require hospitalization. Over the next 2-4 weeks, the donor cells replace the host marrow function and begin to “reject” the CLL cells. This is because the immune system of the donor can recognize differences in the host cells and attack them.

While this may eliminate the CLL, it can also cause “graft-vs-host disease” (GVHD), where the immune system of the donor also attacks other organs such as the GI tract, liver or skin.
The CLL Research Momentum generally features articles that focus on the hard work and scientific research of our grant recipients. However, several of our readers have been working hard to tell others about the Foundation. The creativity of some of our Momentum readers has generated extra funds to ensure we can continue the grant making process and fulfill our mission of abolishing CLL.

Fundraisers come in all shapes and sizes. One of our donors was honored by a group of his high school friends who host an annual golf tournament. He selected CLL Global to be the recipient of the proceeds garnered from the tournament’s events. Another patient’s family compiled recipes from friends and loved ones to create a heart-healthy cookbook to honor his memory and to raise awareness for CLL. Some contributors have simply conducted individual campaigns on our behalf to their family, friends and community. CLL Global happily provides informational materials for volunteers to distribute as they see fit.

One of our supporters, Dr. Ed Jaffe is currently preparing to climb Mount Kilimanjaro, the highest peak in Africa. He is trekking to Africa “to prove that this disease will not keep [him] from living life to the fullest while also raising money to fight CLL.” Dr. Jaffe is well on his way to achieving his $50,000 goal. He has been mentally and physically preparing for several months and is set to depart on July 21, 2011.

Brian Goldman shows his support by sporting the CLL Global logo on his race car. He has been competing in vintage races for several years, but has recently been preparing to start more competitive racing with Sports Car Club of America (SCCA). After he qualifies at the regional level, he and his wife plan to pack up their motor home with the intent to race nationally. His creative thinking will expose CLL Global to a broader group of people who might not be familiar with CLL or our Foundation.

Donations in lieu of gifts for birthdays and special occasions are also requested by some of our supporters. One way to do this is through the Causes application on Facebook. Three Causes have been created by those in the community looking to bring further awareness to CLL. In addition, CLL Global has created a Cause. We are all working together to raise awareness and funds for CLL research.

The Internet is utilized in areas other than social media to raise money. It provides a valuable resource for people and organizations to extend their outreach. One CLL Global supporter sells medical textbooks on E-Bay through missionfish.org, contributing a percentage of the profits to CLL Global. Another useful Internet tool is the search engine goodsearch.com. By selecting CLL Global as the charity of choice, internet searches and online purchases generate funds for CLL research.

Each time you read the Momentum you are also benefitting from the kindness of one our supporters. Davis Brothers Publishing Company has graciously provided the printing for our publication which we hope provides you meaningful updates on CLL research.

We at CLL Global are humbled by the generosity of others who volunteer their time and effort to help. Thank you to everyone who has stepped forward to help solve the CLL puzzle in their own way. We cannot do it alone. Ideas and suggestions are always appreciated. If you are interested in helping the cause, CLL Global will assist with informational materials. To get involved, feel free to contact us at info@cllglobal.org.

To prevent GVHD, patients are required to take immunosuppressive medications, usually for the first 6 months post transplant or longer. Both GVHD and its treatment can further increase the risk of serious infections, leading to the major complications of transplant.

Even patients with high-risk CLL appear to respond to the transplant. This is known as “graft-vs-leukemia (GVL)” activity when the grafted immune cells attack the CLL cells. The initial series of patients with CLL transplanted in Seattle all had fludarabine-refractory CLL.

Earlier studies demonstrated that when a patient’s CLL becomes refractory to treatment, the outcome with conventional therapy is poor with average survival of only 1-2 years. With transplant, survivals have increased to about 50% at 5 years in this population. There are significant risks, as 15-25% of patients receiving allogeneic transplant may encounter life-threatening conditions from non-CLL causes relating to GVHD or infections in the first 3 years. However, this must be placed into the context that infection/complications are the major cause of death for CLL patients who do NOT have a transplant.

The successful control of CLL in our patients largely depends on how much CLL is present at the time of transplant. Patients with bulky lymph-nodes (greater than 5 cm) have had a worse outcome. For the transplant to have the greatest chance of success, it should be considered before there is bulky refractory disease. Age is no longer as important, and transplantation can be considered in patients in their 70’s. There are interesting drugs on the horizon that may improve the outcome of patients with bulky refractory CLL. Drugs such as the tyrosine kinase inhibitors CAL-101 and PCI-32765 may be able to mobilize CLL cells from lymph nodes into the circulation where they are more sensitive to killing by the donor immune system. Clinical trials with this approach are being planned.

Lastly, while many patients with CLL do have an indolent disease and course, those with relapsed disease or high risk genetic markers (17p deletion) should have candid discussions regarding their prognoses with their physicians, and if interested, be referred to a transplant center. Successful treatment of CLL requires a careful balancing of risk vs. benefit. Transplant should no longer be thought of as only a last resort option.

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