



THE INTERSECTION BETWEEN passion & means

CLL Global board member, Robert Nichols, stated at a prior meeting, "We have to find the intersection between the passion and the means." This applies to both our supporters and the research community. Investigators have long had a vision and a passionate commitment to eradicating the disease, but the resources to get there are becoming more and more difficult to achieve. The world recession has hindered philanthropy. Research funding from governments and some charitable organizations is more difficult to obtain. We are still waiting to see the impact of sequestration.

CLL Global has maintained a level of support for CLL research during these troubling times. Fortunately, the means has come thanks to the people reading this newsletter. Large and small, your donations are the reason we can revel in CLL Global's success. Big things are happening as you will read throughout this issue. With true excitement, I can say that the progress is like nothing we have seen before.

The explosion of genetic research has moved us closer to realizing our vision for CLL. When we know the whole genetic pattern of CLL, we will know the best targets and can adjust new treatments accordingly. We already have a tremendous

amount of genetic data, but the cost is very high to translate the data into usable information. The challenge will be considerable to find the genes and the drugs which are most likely to be effective. However, this is a challenge that we readily accept, knowing that the results will change how we view and treat CLL.

We are devoting resources to a variety of genetic subgroups. In particular, we are looking at those patients who have been in remission for long periods of time but continue to present with a clone of CLL cells.

It is uncertain if this family of cells will lead to a recurrence of disease or if these may be dormant cells, unable to reproduce. Either way, we must push for methodologies that completely eradicate the disease and prevent its reoccurrence.

We are now in a unique position where we have dramatic new tools to investigate and to treat CLL. Making the most of these tools requires a total commitment from everyone. I will be waiting for you at the intersection of passion and means. I will bring the passion, and you bring the means. Keep reading so we can further convince you of the progress being made and the opportunities ahead. ::

~ Dr. Michael Keating

I have been a cancer researcher for quite some time. I have been involved in significant research discoveries, and I have watched others develop innovations I never fathomed. The nature of discovery has influenced how I serve as president and CEO of CLL Global. I believe in the power of discovery and have remained devoted to the organization's mantra "money in, money out." We do not have an impressive stock pile of funds. As the funds come in, we commit them to specific projects.

We like to be flexible in our thought process to ensure we are ready to jump on a good opportunity. In addition to grant funding, CLL Global has provided seed funding for CLL collaborative research programs, educational activities and infrastructure support to advance CLL research. We are proud of our accomplishments but realize there is always more to do.

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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.

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CROSS TALK WITH Dr. Neil Kay

Dr. Neil Kay (Mayo Clinic) recently completed his CLL Global Alliance project focused on the microenvironment (the physical space in the bone marrow where CLL cells reside), with its complex network of physical and chemical signals, and how it affects the proliferation rate and survival of CLL cells. We sat down with Dr. Kay to discuss CLL research and the findings from his project.

HOW DID YOU BECOME A CLL RESEARCHER?

I gravitated toward CLL research for two reasons: 1. It was and is a great model to study human malignancies and malignant processes 2. My first academic appointment in the U.S. was at a Veterans Affairs hospital where there were large numbers of CLL patients who were very gracious in providing blood samples for my work. The ability to have blood samples and marrow samples from many CLL patients where I could also document their subsequent clinical course facilitated my interests in doing long term studies of CLL. I have been doing it since the mid to late 70s and I have never lost interest.

PRESENTLY, WHAT IS THE MOST PROMISING ASPECT OF CLL RESEARCH?

Right now, I would say, apart from some of the novel signal inhibitor clinical trials, we are most interested in the interaction or "cross-talk" that is going on between leukemic cells and their microenvironment. I believe that we will need to determine the most important aspects of this cross-talk and how to block it as this would likely have a significant impact on understanding disease progression and allow for novel therapy approaches.

HOW HAS YOUR CLL GLOBAL ALLIANCE PROJECT TRIED TO UNDERSTAND THE CROSS-TALK?

Our work has been directed at how leukemic cells or their secreted products influence and effectively educate nurturing tissue sites. Our first goal was to develop a culture system that allows us to grow and maintain tissue cells from CLL and normal individual host sites. We used mesenchymal stem cells (MSC) which make up an important component of the tissue from normal bone marrow.

IN LAY TERMS, WHAT ARE MSC?

They are a type of stem cell that resides primarily in the bone marrow. We think they are an important

component of the stromal system [or microenvironment] that helps CLL B cells survive and even remain in what we call a "minimal residual disease" status. We are able to acquire the MSC cells directly from the bone marrow and keep them in a steady state in the lab in order to characterize their biologic features. By combining leukemic cells from patients and their MSC, we have found that two types of cells are able to talk to each other and influence each other's behavior. For example, the MSC generate a longer life span for the leukemic cell and confer enhanced drug resistance. Being able to co-culture MSC cells with CLL cells was our first step in developing a primary marrow model in the lab. We are now incorporating other cell types to better mimic the bone marrow. Eventually, we should be able to get a much more integrated stromal model system.

HOW LONG HAS THE STUDY OF CLL AND STROMAL CELLS BEEN GOING ON AS OPPOSED TO JUST CLL CELLS?

I would say one of the seminal studies was Tom Kipps and Jan Burger's nurse cell studies. There had been other indirect studies prior to his, but I think those observations were the real launching pad for the subsequent work on cross-talk or communication between CLL cells and their microenvironment.

HOW MIGHT THE CROSS-TALK BE BLOCKED

We are looking at ways to block the dialogue between leukemic B cells and their stromal cells in order to blunt the stromal function. In this regard we have recently found tiny packets of information called microvesicles in CLL plasma that can bind to stromal cells and transfer activating information. There is really an amazing amount of information contained in these vesicles. From our microvesicle studies, we have found a certain receptor that is present on both CLL cells and MSC. We have access to novel inhibitors of this receptor. We have recently tested these inhibitors and found them to be very robust in killing CLL cells. This finding will lead to novel clinical trials in CLL patients using these

receptor inhibitors. In addition, we have now standardized how to test for and measure levels of microvesicles in CLL patients. We have detected that there are elevated microvesicles prior to therapy in CLL patients and are now looking at them over time. So we are literally using plasma microvesicles as an indicator for residual disease, and we think it may be more sensitive than traditional tests. For example, if a patient has had a complete response after six months of therapy but still has large amounts of these microvesicles in their plasma, we would be concerned that this patient still has disease and would relapse quicker.

WHAT HAS SURPRISED YOU DURING YOUR CLL GLOBAL PROJECT?

There are a couple of things. One is that we have been able to define a relatively restricted set of mechanisms that may be very important in terms of the interaction between leukemic cells and MSC.

We originally thought a multiplicity of factors was turning on MSC but it turned out to be relatively restricted. This encourages us to think we can use a single agent to block that activity.

The other thing that has been very striking is finding out that the CLL MSC is very different from the normal MSC. This was a surprise to us. You would not think that a stromal cell was part of the malignant process, but it is. When we take MSC from an age-matched healthy individual without CLL, we find the MSC from the CLL and non-CLL patients are very different by both functional and genetic analyses. It is a bit of a surprise to us but does indicate that the CLL cells are educating the stromal cells to be different. Given this, we are actually interested in determining if effective therapies for CLL patients not only get rid of the leukemic clone but actually normalize the stromal cells in the bone marrow of CLL patients.

IS ANYTHING YOU LEARNED ALREADY APPLICABLE TO PATIENTS?

What is applicable to patients right now is that we are currently testing stromal function in clinical trials. In other words, we are characterizing patients not just on their leukemic clone and their disease stage, but on the capacity of their stromal function. We want to study their stroma before and after treatment to see if it has normalized.

HOW HAS YOUR CLL GLOBAL GRANT BENEFITTED YOUR RESEARCH?

There is no question that our work at Mayo has exponentially benefited from CLL Global's support. It has allowed us to explore areas we would not have been able to otherwise do in any systematic fashion. Based on CLL Global's support, we have also applied for and received grants that supported and amplified the CLL Global work. We have also been able to get some junior people grant awards because of this support. So I can truly say the support for us has been very positive. ::



READING THE tea leaves

exploring EGCG in combination with other drugs, so we hope to ultimately test EGCG in some combination. The bottom line is that phase I and II has showed EGCG to be safe and effective in reducing the burden of disease for early stage CLL patients. We are very interested in continuing this work, and hopefully we can get to a phase III trial.

HOW DO YOU RESPOND TO PATIENTS THAT WANT TO TAKE GREEN TEA FOR THEIR CLL?

I cannot recommend this because I do not know what is in the over the counter products they are buying. On the other hand if they want to just drink green tea instead we would estimate that they would have to drink more than 15 cups a day to reach an effective dose level of EGCG. What we do recommend is vitamin D. We have found that vitamin D insufficiency is associated with a faster time to need for therapy and overall survival in CLL patients. We are now conducting a phase III clinical trial normalizing vitamin D levels in deficient CLL patients to see if this will truly improve their clinical outcome.

WHY DO CLL PATIENTS HAVE A VITAMIN D DEFICIENCY?

One issue, especially for people in cold, northern climates is they don't get a lot of sun exposure. We recommend avoiding the sunlight because of the increased incidence of skin cancer. However, that can make the vitamin D deficiency worse.

So having patients take the vitamin D actually gets around that.

CAN YOU TELL US MORE ABOUT THE STUDY OF VITAMIN D IN CLL?

There is now a phase III trial for vitamin D replacement at Mayo. This trial will be for Rai 0-1 CLL patients where if their serum vitamin D level is below a certain value they will be randomized to be given replacement Vitamin D or placebo for 12 months. This group will be compared for clinical outcome to another CLL group of early stage that has higher vitamin D levels and will be observed. The hope here is that this trial will show that vitamin D replacement can delay the need for therapy and improve survival.

HOW FEASIBLE DO YOU THINK NATURAL/HOMEOPATHIC OPTIONS ARE FOR PREVENTION/CURE?

The tendency is to dismiss these options because they are routinely never tested in clinical trials. However in my opinion we should be paying attention to any anecdotal reports because there are many documented instances where patients are taking certain alternative therapies and get better. Some of it seems hard to believe, but if these compounds are available for safe testing and you can validate these through appropriate clinical trials, it seems to me that it is something we should be thinking about. ::

In addition to Dr. Kay's Microenvironment Alliance project, CLL Global previously supported Dr. Kay's research using an oral green tea extract.

In the initial study, asymptomatic patients were given varying doses of epigallocatechin gallate (EGCG), a major component of green tea. The majority of patients had a reduction in lymphocyte count and decline in lymph node size. Subsequently, Dr. Kay and his colleagues conducted a second study with similar findings. CLL Global often receives inquiries from patients about the status of EGCG research. So we continued the conversation with Dr. Kay to find out.

DO YOU STILL ACTIVELY STUDY EGCG?

We completed and have now published the phase I and II clinical trials of EGCG. These latter trials involved early stage non progressive CLL patients. We had a phase III trial of EGCG vs placebo with a cross-over option planned but for a variety of reasons the study was not implemented. Some of the issues regarding continued support for this trial included the fact that patients can buy tablets of EGCG containing products over the counter. We continue to do laboratory testing with EGCG and we are now

WHAT REMAINS ON our to do list?

We have dedicated many articles in past issues of *CLL Research Momentum* to research successes. There have been major advances in patient survival; new agents and technologies advancing through clinical trials; and an abundance of information generated on genetic factors. With all of this progress, we started thinking about some of the remaining items on the CLL To-Do List. ::

❑ **Identify better therapeutic options for certain sub-groups of patients.**

Older patients, particularly over the age of 75, have not been included to a large extent in clinical trials. This has resulted in a dearth of information on the best treatment approaches for this population. In addition, patients who have an abnormality in the 17p chromosome are not well served by chemotherapy; so specific targeted approaches are needed to improve their outcome. Patients who have partial deletion of chromosome 11 have a very good initial response but almost all relapse. (Fortunately, there is a high second response rate.) The elderly, 17pdel- and 11q- are just three of the groups that need better therapeutic options. See page 5 for more information on ongoing efforts in these three populations.

❑ **Expand access to clinical trials, particularly for CLL patients with additional conditions.**

One amazing anomaly of clinical trial access is that patients who have had a previous cancer within the last five years are usually excluded from clinical trials. Physicians should be able to identify which patients are likely to benefit from treatment and which cancers constitute a higher-risk. Additionally, to start on a clinical trial, patients need to have a favorable performance status which often rules out those who have other comorbidities such as cardiac disease, chronic obstructive airway disease, diabetes, etc.

Clinical trials are conducted in a very controlled environment; patients must meet the outlined criteria for entry. However, when new drugs are approved, the agents become broadly available but physicians lack experience on how to use these drugs in patients with comorbidities. Expert centers need to gain experience treating patients with comorbidities, previous cancer, marginal kidney and liver function in order to advise community physicians as to whether these regimens can be administered safely to these subsets of patients.

❑ **Develop strategies to prevent the immune system from destroying cells.**

A number of CLL patients develop antibodies that attack and destroy red cells, platelets and to a lesser degree neutrophils. One of these conditions, immune thrombocytopenic purpura (ITP), results in dangerously low blood platelet counts. We need to better understand which patients are likely to experience ITP and which treatments are most effective in overcoming this problem. Current options include high-dose steroids, platelet-stimulating agents, immunosuppressive drugs and chemotherapy agents alone or with the monoclonal antibody, rituximab. A newer antibody, velutuzumab, which targets the same protein as rituximab is in clinical trials for managing ITP and CLL.

Romiplostim (subcutaneous injection) and eltrombopag (oral agent) are used to overcome the low platelet count caused by these rogue antibodies. Removal of the spleen, usually the site of antibody damage, is often another treatment option. The development of laparoscopic procedures has markedly improved the ability to control this complication without major operative consequences. Some patients do not respond to splenectomy and will require further therapy. Although there are a variety of treatment options available many only produce short-term responses. We need to improve our understanding of this condition and find ways to predict which treatments will be most useful for patients.



❑ **Prevent treatment-related damage to the immune system and DNA.**

A significant number of CLL patients will die of an associated malignant disease which develops after treatment or from serious infections presumably related to the immune system. One of our goals is to remove DNA damaging drugs from the patient's initial therapy. Hopefully, this will keep a number of patients in long term remission without running the risk of the second cancers including secondary acute leukemia or myelodysplastic syndrome (MDS). In the future, we also hope to be able to restore the immune system if it has been damaged by treatment or has not recovered satisfactorily after therapy. Therapies that address the immune system are critical; clinical research on these strategies needs to be accelerated.

❑ **Reduce the likelihood of CLL patients developing shingles.**

A major irritation for many CLL patients is that they have a very high likelihood of developing shingles. No one wants to deal with the itching, tingling and severe pain often associated with shingles caused by the varicella zoster virus. For most healthy individuals, the recommendation is to be vaccinated with a live, weakened virus. However, CLL patients and other individuals with weakened immune systems are advised to avoid vaccination with a live virus. The concern is that patients may develop modified "shingles" from the vaccine virus strain; no research has been conducted in CLL to evaluate this possibility. Alternative protection strategies need to be developed for CLL patients and others with compromised immune systems. One strategy in development is to use the immune modulating drug called lenalidomide to improve the response to vaccinations.

As you can see, major, unresolved issues persist but you can be assured that there is going to be a vigorous approach to addressing these concerns and many more. The ultimate result should be improved duration of survival and quality of life for CLL patients. ::



LET'S CURE CLL CAMPAIGN EXCEEDS GOAL

THE SEARCH FOR THERAPEUTIC OPTIONS -

moving in the right direction

The goal of therapy is to find the right treatment for the right patient at the right time. Many sub-groups of CLL patients require additional research to improve therapeutic options. Below we feature the work being done on three particular groups.

1) ELDERLY

Elderly is generally defined as 65 or older. This is somewhat unrealistic for CLL where the median age of diagnosis is 72 years. The elderly represent the majority of new CLL patients. Traditional chemoimmunotherapy regimens are often considered too aggressive for elderly patients. Many patients over the age of 65 are in excellent physical condition and are likely to benefit from chemoimmunotherapy; however the downside of chemoimmunotherapy is suppression of the immune system and the risk of developing second cancers. Thus, a number of institutions have elected to develop chemotherapy-free treatment programs for elderly patients

Traditionally, the elderly have been excluded from clinical research. Fortunately, age is increasingly being removed as exclusion criteria. However, elderly are more likely to be excluded based on other comorbidities. It is important to understand how new therapies will work in the elderly, particularly because they represent the majority of CLL patients and there is so much uncertainty as to which elderly patients will benefit from chemoimmunotherapy. Many of the new oral agents in development are not likely to cause DNA or immune system damage making them particularly suitable for the elderly. Several studies are now being designed specifically for older patients. For example, there is an ibrutinib vs chlorambucil randomized study specifically for treatment-naïve patients 65 or older.

Since most CLL patients fall into the 65 or above category, we started by looking at this sub-group. For all of our friends that do not fall into this category, we will be working on a future article that looks at research being done in younger patients. Many of you may also fall into one of the categories below.

2) 17p DELETION

Clinicians and patients are most certainly in need of new treatment options for those with 17p deletion. Chemoimmunotherapy regimens are often not effective in 17p deleted patients. Having a deletion on the short arm of the 17p chromosome usually correlates with a mutation of the p53 protein which is responsible for many of the proteins that influence cell survival or cell death. Fortunately, many of the new agents in development such as BTK, PI3Kdelta, and BCL-2 family inhibitors appear to be very active in patients with a dysfunction of p53 (17p deleted). Recognizing the important unmet medical need, many pharmaceutical sponsors are adding cohorts or studies specifically looking at the 17p deleted patients.

3) 11q DELETION

Patients with an 11q deletion have dysfunction of a very important enzyme, ATM. This deletion is also considered a high-risk genetic abnormality. Several research labs are now working on inhibitors of pathways associated with ATM. Research has shown that patients whose ATM does not work have CLL cells much more sensitive to particular therapeutic approaches. An ongoing study of the oral drug sapacitabine in combination with chemotherapy has shown in initial results the ability to selectively kill off cells that have poor function of the ATM protein.

Research is clearly headed in the right direction. The CLL community is more intelligent and more focused than ever before; ongoing research promises to minimize side effects of patients and improve long-term outcomes. ::

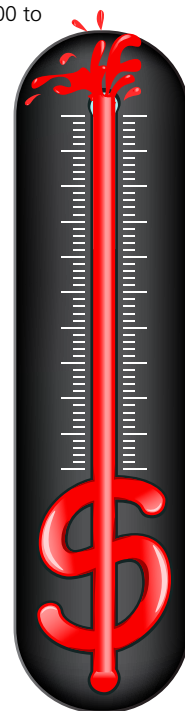
We at CLL Global are so very grateful for the big-heartedness of our supporters who give time and effort to help the cause. One of our long-time donors, Carol Preston, created an online giving campaign for CLL Global during the 2012 holiday season. Carol has a very personal reason to be involved. She is a CLL survivor and would like nothing more than to send this disease packing!

Carol contacted our office in October 2012 declaring "I want to raise money directly for the CLL Global Research Foundation". She had raised funds previously for another blood cancer organization but learned that only a small portion was earmarked for CLL. She wanted the majority of the money she raised to be used specifically for research to eradicate CLL.

Carol put together her email list of friends, family and colleagues, hooked up with an online charitable giving website and her campaign "Let's Cure CLL!" took off. In addition to email, Carol enlisted social media like Facebook to get the word out. She successfully brought in over \$5,800 to CLL Global, far surpassing her original goal of \$2,000, an outstanding achievement!

You, too, can host your own fundraising campaign and encourage your friends and family to support the cause. There are many creative ways to raise money beyond writing a check. Give us your ideas, and we will be ready to assist you.

Thank you to everyone who raises money to battle leukemia, specifically CLL. Remember, we are in this together. And together, we can fund the research that soon will lead to a cure. ::



MEET OUR NEW grant recipients

CLL Global recently selected four new grant recipients to receive \$100,000 each to conduct CLL research. With the announcement of these grants, CLL Global surpassed the \$19 mil mark in grant support toward chronic lymphocytic leukemia (CLL). The first grants were given out eight years ago. The consistent element of each of the funded projects is the desire to accelerate research and to provide clinically relevant information within two to three years. CLL Global is grateful to its Scientific Advisory Board and our external reviewers for their thoughtful consideration of the submitted applications. We are pleased to introduce you to our four new recipients.



Dr. Rosa Bernardi (San Raffaele Scientific Institute, Milan, Italy) is evaluating the role of oxygen reduction in the cellular environment on the development and progression of CLL. She wishes to understand the contribution of hypoxia-induced signaling (decreasing oxygen) towards regulating cell survival mechanisms. The ultimate goal is to develop new

therapies for CLL which target this pathway.

Dr. Bernardi and colleagues are studying a specific group of proteins called Hypoxia-inducible transcription factors (HIFs). These proteins play a role in the regulation of gene expression in response to low oxygen levels in the cellular environment. When oxygen decreases occur, these proteins induce a wide array of responses, ranging from new vessel formation to metabolic adaptation and cell migration. Because this group of proteins is increasingly associated with the development of solid tumors and some hematological malignancies, Dr. Bernardi's team is interested in inhibiting these proteins as a potential cancer treatment.

The specific protein HIF-1 α is highly expressed in CLL cells compared to normal B cells. This protein has been suggested to stimulate new vessel formation and resistance to cell death. Bernardi hypothesizes that compounds with HIF-inhibitory activity may also promote the release of CLL B cells from their protective environment, exposing them to the toxic effects of chemotherapy.



Dr. Asish Ghosh (Mayo Clinic) is studying the role of extracellular vesicles in CLL progression and therapeutic outcomes. These vesicles alter stromal cell (microenvironment) function; modulating stromal function is likely to enhance the progression of CLL. Dr. Ghosh and colleagues will examine various attributes of the microvesicles as CLL patients

progress through their clinical course and treatments. Ghosh participated in the work performed under Dr. Neil Kay showing that microvesicle levels fluctuate during therapy (See page 2).

Ghosh predicts that patients with an increase or constant microvesicle level will relapse more quickly because of the microvesicles' ability to modify host stromal function. Ghosh and his colleagues will attempt to understand how the microvesicles change stromal cell function. They will look particularly at specific non-coding RNAs (small genes that regulate the expression of proteins.) Information learned from this research should enhance our understanding of and ability to prevent disease progression.



Dr. Graham Packham (University of South Hampton, United Kingdom) is examining the communication between the B-cell receptor and proteins on the surface of CLL cells. The B-cell receptor (BCR) is a specialized protein that sits on the surface of CLL cells. It can detect cues from outside the cell and trigger responses within the cell that promote the

survival and growth of leukemic cells. The BCR also communicates with other proteins on the surface of CLL cells, including CXCR4, which helps to control how CLL cells move around the body. Packham's project will investigate the mechanisms that CLL cells use to allow communication between the BCR and CXCR4. By studying these pathways, they hope to identify markers that can be used to select optimal treatment regimens for patients and possibly to develop new treatment strategies to interfere with BCR/CXCR4 communication.



Dr. Alfonso Quintas-Cardama (MD Anderson Cancer Center) is looking at patients with chromosome 17p deletion. This is considered a high-risk group of CLL patients. (See page 5). In general, these patients fail to respond to standard treatment and have poor outcomes. Loss of 17p is often associated with a mutation in the p53 gene, an important gene in

predicting the effects of chemotherapy and radiation. The p53 mutations are detected in 7–9% of newly diagnosed CLL patients and in 30–40% of patients who have failed frontline chemoimmunotherapy. Recently, ibrutinib, an inhibitor of the Bruton's tyrosine kinase (Btk), has shown preliminary activity in CLL with 17p-.

Dr. Quintas-Cardama and colleagues will use a genetically engineered mouse model with and without p53 mutations to study the impact of the mutation on response and survival. His group will study responses when conventional (fludarabine) or Btk inhibitor (ibrutinib) therapy is used.

In addition to the mouse model, the group will study the signaling and activation response of B-CLL cells obtained from 17p- patients receiving ibrutinib. The results from this study could be extended to other high-risk B-CLL patient populations and may facilitate combination approaches using ibrutinib. ::