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CLL RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – ALLIANCE SPECIAL EDITION

SUMMER 2008

A "BLITZ" ON CLL:

United toward one goal

The CLL Global Research Foundation (CLLGRF) has funded 31 individual, peer-reviewed grants over the last four years, totaling $5.3 million. All of these grants have produced new information and insights, and many have led to further grant support from other agencies. Our research funding is already moving new drugs into the clinic.

We have funded excellent grants; however, the research is performed in specific isolated projects or "silos" rather than in an integrated fashion. After evaluating the impact of our grant program, I developed and presented to my mentor and member of the Board of Directors, Dr. Emil J Freireich, an initiative to integrate research on the five big ideas in CLL research. His opinion was that "while patients who are donating funds for the research would love for us to understand CLL, they would more likely prefer for the understanding to come after curative treatment has been developed." Always a quick learner, I decided to change the initiative to the five big "treatment concepts" in CLL. Thus, the U.S./European Alliance for the Therapy of CLL (Alliance) was born. The five thematic areas are:

CLL ALLIANCE

1. **Gene and Vaccine Therapy**
2. **Transplantation or cellular immunotherapy and reconstitution of the immune system**
3. **New drug development and clinical trials**
4. **Antibody development and measurement of minimal residual disease**
5. **Understanding the role of "stroma" in supporting CLL cell survival**

Twenty-five experts were asked to participate in one of the five working groups. Each of the groups convened, under the leadership of a working group leader, to identify areas ripe for exploration and integration. Twenty projects have been evaluated and funded (totaling $2.98 million). There is a close interaction among the twenty different grants with overlapping areas of interest. The Alliance structure provides an opportunity for collaboration which will accelerate research and our understanding of how to treat this disease. The group of Alliance participants represents most of the leading figures in CLL research.

This is an extremely ambitious program. We have invited and received acceptance from many of the premier CLL investigators in the world who are committed to working together to eradicate CLL. We had our first U.S./European joint meeting in Italy in June. This proved to be nothing short of exhilarating, as new research was presented and unique collaborative ideas were generated. The Alliance represents a surge in our efforts to accelerate CLL research. Combining our Alliance, individual peer-review and other grants, we have awarded almost $9 million in grants over the last four years.

In this issue of the Momentum, we will introduce some of the Alliance projects and the researchers who are working on pieces of the CLL curative puzzle. We look forward to sharing additional information on the Alliance with you as we progress. We know that the Alliance will provide substantial momentum to succeed in the battle against CLL. : :

Dr. Michael J. Keating

Dr. Michael Keating, Professor of Medicine at M. D. 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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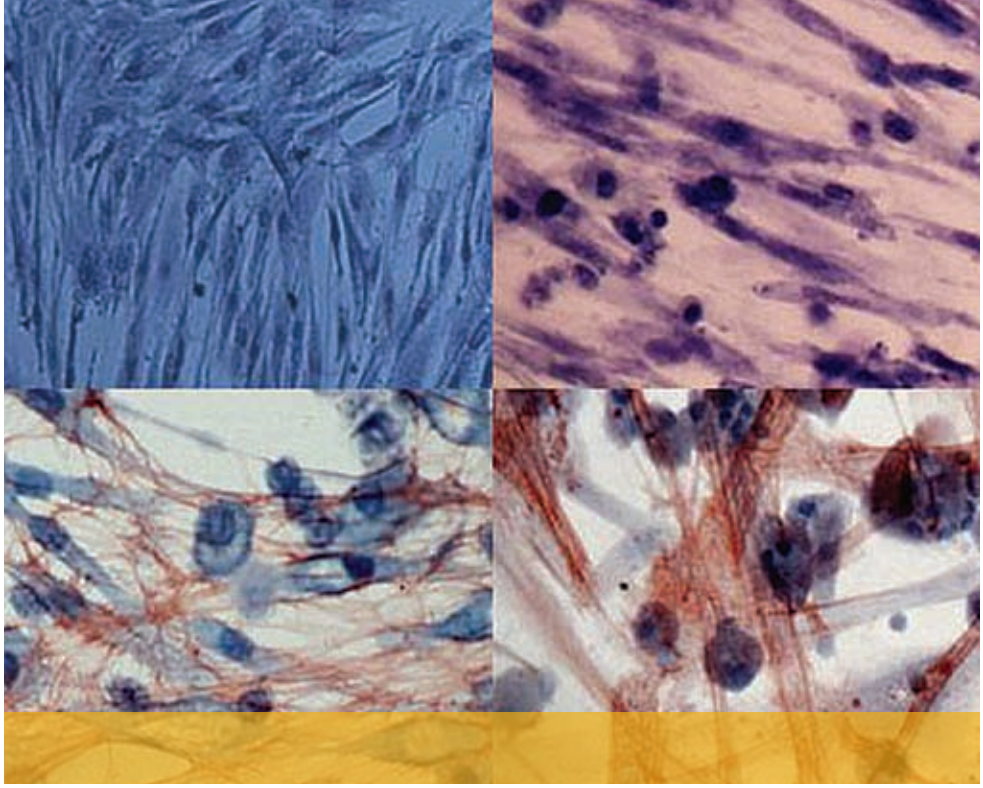

TARGETING THE PROTEIN

keeping CLL cells alive

Cancer cells generally grow rapidly, and therefore, many cancer strategies have targeted the cell division process. In contrast, CLL cell growth is relatively low and CLL therapeutic strategies concentrate on killing slowly growing CLL cells.

CLL cells undergo cell death (or apoptosis) when the cell death pathway is functioning. When this pathway becomes ineffective, CLL cells continue to survive and cause harm. The presence and over-expression of a family of proteins (anti-apoptotic proteins) disrupts the cell death pathway allowing the survival of CLL cells. These anti-apoptotic proteins bind to other proteins (pro-apoptotic proteins) at a specific site (the BH3 domain). Because these pro-apoptotic proteins that favor cell death are blocked, the cell death sequence of events is prevented. A certain class of agents (BH3-mimetics) is capable of binding to the anti-apoptotic proteins, leaving the pro-apoptotic proteins free to do their job of causing cell death.

Dr. Varsha Gandhi and Dr. Kumudha Balakrishnan hypothesized that BH3 mimetics will induce CLL cell death. As a proof-of-principle study, the M. D. Anderson group began with gossypol, a cotton seed plant derivative which acts as a BH3-mimetic.

Using a mixture of two forms of gossypol and using CLL cells isolated from peripheral blood, the group demonstrated (1) gossypol treatment resulted in a decline in the cell's energy pool, (2) there was a disruption in the mitochondria (site of cell energy production) and (3) due to disrupted mitochondrial membrane there was a release of an enzyme (cytochrome c) and other apoptosis inducing factors to other parts of the cell. These sequential events lead to gossypol-induced CLL cell death.

The group is currently working with AT-101, which is being developed by Ascenta Therapeutics. AT-101 is a form of gossypol that is more potent to cancer cells and less toxic to normal cells. Dr. Gandhi and colleagues are also extending the studies to other analogues of gossypol. Eventually, the most effective compound will be tested in the clinic for CLL patients. Other drugs which act on BH3 are also in clinical trials. ::

CELLULAR SIGNALS IN CLL- FINDING THE mute button

In CLL, there is a fatal attraction between the leukemia cells and "feeder cells" that are present in lymph nodes and the bone marrow. These feeders, also called nurse-like cells or stromal cells, provide CLL cells with nutrients and drug-resistance signals. At the first meeting of the U.S./European Alliance for the Therapy of CLL in Lake Orta, Italy, experts in this emerging field discussed new ways to determine which molecules are important for this interaction between CLL and the feeder cells, and how to find novel drugs to target the nourishing nurse cells.

Dr. Zeev Estrov, M. D. Anderson Cancer Center, presented his laboratory work that investigates the role of stromal cell-derived signals for activation of transcription factors called STATs. Dr. Estrov's group found that STAT-3 is persistently activated in CLL cells by environmental signals. Because STAT-3 blocks leukemia cell apoptosis, STAT-3 presents an attractive target for drug discovery. Dr. Neil Kay, Mayo Clinic, presented his research about the function of bone marrow stromal cells in CLL disease progression. In CLL patients' marrow, these cells form "niches" for CLL cells and within these niches CLL cells can survive the attacks by chemo- and antibody-therapies.

Dr. Federico Caligaris-Cappio, Instituto Scientifico San Raffaele, presented new data about the role of a molecule called HS1. HS1 in CLL cells is important to connect signals from the microenvironment, such as stimulation with antigen, to activation of the cytoskeleton of the leukemia cells. Dr. Jan Burger's group, in collaboration with Drs. Gandhi and Plunkett (all at M. D. Anderson) is developing standardized laboratory tests in which CLL cells are cultured with different types of feeder cells and then exposed to various drugs such as fludarabine.

Previously, drugs for treatment of CLL were tested in the laboratory without feeder cells, not taking into account the drug resistance signals that CLL cells receive from the feeder cells in patients (in vivo). Dr. Burger discussed how to establish and standardize these new tests in order to make them available to CLL researchers around the globe. Also, this effort will help to predict how new drugs will work in tissues such as the bone marrow and the lymph nodes. Dr. Burger also presented collaborative research with Dr. Andreas Rosenwald, Würzburg University, Germany, in which lymph nodes and marrow samples from CLL patients will be characterized for presence of feeder cells. Drs. Burger and Rosenwald are also analyzing the signal responses in CLL cells to the presence of stromal cells by microarray studies, a technique that Dr. Rosenwald has pioneered. These studies will help to discover new drugs that target the cross talk between CLL and stromal cells.

Collectively, the research implemented by the Alliance will define the anatomy, signaling pathways and new therapeutic targets in the CLL microenvironment. The first clinical trials for CLL and other leukemia patients with drugs that target the stromal-CLL interactions are currently in preparation. These studies, based on the work of the Alliance researchers, are expected to open in 2009. ::

Members of the CLL-Stroma group, Drs. Neil Kay and Jan Burger, discuss new drugs that target the CLL cell's microenvironment with Dr. Michael Hallek, member of the New Drug group.

ORTA 2008-AN ADVISOR'S ACCOUNT

The meeting organized by the CLL Global Research Foundation in June in Italy was a huge success. Dr. Keating's group was able to get virtually every important physician-scientist who is studying CLL in the U.S. and Europe to come to the meeting venue on Lake Orta for an in-depth evaluation of what advances have recently occurred and what new directions should be taken in the near future with the aim of quickly finding a lasting cure of this disease. The presentations were kept extremely brief because everyone in attendance was a recognized expert in CLL, and each speaker only had to report what progress of any significance has been made in each of the several areas in this field. This was then followed by spirited, yet thoughtful discussion, geared towards treatment of CLL.

In my opinion, this meeting turned out to be a great success because the meeting organizers chose to start with the topic of CLL-Stroma Interaction. This is a topic which is likely to be extremely important in developing new ideas in treatment of CLL, and yet at most other meetings of similar nature, this topic comes last on the agenda, when people have already been at work thinking about CLL for hours and there is an undeniable fatigue setting in.

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COUNTING CLL CELLS WITHOUT a microscope

The majority of CLL patients initially treated with modern chemoimmunotherapy regimens, such as FCR (fludarabine, cyclophosphamide and rituximab), will achieve a complete remission (CR). CR implies no evidence of disease upon physical examination or in blood/bone marrow test results. Patients with no CLL cells or DNA are classified as minimal residual disease (MRD) negative. Clinical trials suggest that MRD negativity prolongs the duration of the patient's response and improves survival.

For those patients whose response is short-lived, researchers are looking to develop an intervention strategy based on the measurement of residual cells in the blood, bone marrow and plasma. This may provide a comprehensive measure of the total CLL burden in the body.

Measurement of residual disease is problematic in that many of the cells may remain hidden in the lymph nodes and spleen even when disease is not detectable in the blood and bone marrow. Recent studies show that proteins present on CLL cells may remain at high levels in the plasma (fluid surrounding blood cells in the bloodstream). A patient is more likely to have disease recurrence with a higher level of detected proteins. As CLL cells degrade, the DNA is broken down into smaller, detectable fragments in the plasma.

Using CLL DNA in the plasma may prove to be a more feasible, cost-efficient method for quantifying residual disease.

Over the last ten years, the focus has been on detecting remaining CLL cells in the blood and bone marrow. Flow cytometry and polymerase chain reaction (PCR) techniques have been used to detect 1 in 100,000 CLL cells. The normal PCR technique is cumbersome. Genes must be sequenced and the specific primers, or enhancing molecules, must be developed for each patient. With flow cytometry, individual cells must be counted and examined for a specific protein pattern to identify the presence of CLL cells.

A simpler PCR method, the ligase reaction, has been developed but is not established as equivalent to the "gold standard" (using the more cumbersome patient sequence specific PCR technique). The MRD group of the Alliance, headed by Dr. Susan O'Brien of M. D. Anderson, will compare the ligase reaction with the traditional PCR technique. Both techniques will be used to measure the CLL DNA in the plasma. By looking at components from the membrane and from the plasma DNA, it may be possible to index the remaining CLL.

Understanding the detectable levels of CLL will influence treatment decisions. Patients with no detectable CLL or with consistently low levels will not be treated. Treatment will be considered for patients with a rising level to eradicate the remaining population of cells. Researchers must evaluate the accuracy and validity of these methods in predicting clinical behavior. The most cost effective and predictable methodology should be applied in academic research centers and more widely in the treating community. : :

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Because of this clever move, we were able to devote sufficient time to this topic while we were all rested and fresh in tackling the new treatment issues. Other important topics, including New Drugs and New Monoclonal Antibodies, also received adequate airing and exploration. Highly promising leads for improving therapy for CLL were presented.

There was a sense of camaraderie and collaborative spirit among the attendees, which is rather different from similar get-togethers of experts in many other diseases where a certain degree of competitiveness and secrecy becomes unavoidable. I give full credit to Michael Keating for creating the atmosphere where free and frank opinions were expressed to either critique or applaud newer ideas presented by participants—such an atmosphere is absolutely an essential ingredient of any successful solution to an otherwise extremely difficult task—finding a cure for CLL.

Kanti R Rai, MD : :

Dr. Kanti Rai is Chief of the Division of Hematology-Oncology at Long Island Jewish Medical Center in New Hyde Park, N.Y. Dr. Rai is a pioneer in the field of CLL research and serves on the Advisory Council of the Alliance.

Dr. Rai and Dr. Stephan Stilgenbauer, member of the Minimal Residual Disease group, discuss the presentations.

RESEARCHERS COLLABORATE TO TACKLE CLL immunity

Researchers in the U.K. and the U.S. are working together to understand CLL immunity. Under an Alliance grant, funded by CLLGRF, groups from both countries are combining their expertise to educate T-cells and assess their function.

It is known that CLL patients have decreased immunity, although the precise mechanisms for this are not yet clear. CLL patients also have an increased number and frequency of infections with low levels of antibodies in their blood. Untreated CLL patients have normal or even increased T-cell numbers. Many of the effective treatments for CLL also lead to a loss of normal lymphocytes and worsen the already decreased immunity. Some treatments, such as alemtuzumab (Campath), lead to near complete eradication of normal B- and T-cells, and this is associated with further immune suppression which can take many months to recover.

In a related project funded by CLLGRF, and now published in The Journal for Clinical Investigation, Dr. Alan Ramsey and Professor John Gribben from St. Bartholomew's in London showed that T-cells from CLL patients have a decreased ability to form immunological "synapses" that are required for normal T-cell activation. They also demonstrated that CLL cells can cause these same defects to occur in T-cells from healthy donors, suggesting that even after allogeneic stem cell transplantation, presence of CLL cells could lead to inhibition of immune function.

At the same time, Dr. Elizabeth Shpall's group at University of Texas M. D. Anderson, using technology developed by Dr. Carl June at the University of Pennsylvania, showed that they could expand sufficient cells for allogeneic stem cell transplant from umbilical cord blood (UCB). In collaboration with the group form St. Bartholomew's, Dr. Shpall's group has shown that the UCB cells seem to be immune from the inhibitory effects of CLL cells. Dr. Shpall has also developed techniques in the stem cell laboratory to be able to expand T-cells in the test tube that can then be frozen and given back to patients after treatment.

Under an Alliance grant, the two groups are now working jointly to use the new assays developed in London to assess how well UCB and expanded T-cells function. Two clinical trials are already planned. Professor Gribben commented that "this is a very exciting initiative and we are very grateful to CLL Global Research Foundation for the opportunity afforded for us to work together collaboratively to tackle CLL. We have already had a number of lab meetings using the internet and have been able to exchange data very easily." Two clinical trials are already planned.

The first clinical trial will involve collecting blood cells from CLL patients before treatment with alemtuzumab. The T-cells are then expanded in the laboratory and frozen. Once the treatment is completed, the cells are thawed and given back to patients to increase the speed of immune recovery. This study will be conducted jointly at the University of Pennsylvania and M. D. Anderson.

Dr. Chitra Hosing at M. D. Anderson is also leading studies exploring the use of UCB transplants in patients with CLL and other blood cancers. This represents a readily accessible source of stem cells for those patients who do not have a matched sibling donor. More laboratory studies are planned by Professor Gribben and Dr. Shpall. The last planned clinical trial will use UCB cells expanded in the laboratory to provide the number of T-cells needed to improve immunity after UCB transplantation and to increase the effect of these cells against CLL cells. : :

BACK TO SCHOOL: RE-EDUCATING

the immune system

Dr. William Wierda, Dr. John Gribben and Dr. Thomas Kipps

The Gene and Vaccine Therapy Alliance Program consists of 3 projects; the overall goal is to develop vaccines for CLL patients. Dr. William Wierda, University of Texas M. D. Anderson Cancer Center, is overseeing the ISF35 gene therapy vaccine project. He is conducting a phase II clinical trial with repeated doses of ISF35, a vaccine he has worked on in collaboration with Dr. Thomas Kipps, University of California San Diego (UCSD), since his fellowship. This project includes laboratory investigations to characterize the immune responses against patients' own leukemia cells mounted by their immune system following vaccination with ISF35. Laboratory investigations of patients treated on the phase I trial will also continue. These studies will enable investigators to understand the immune responses that patients are able to mount against their own leukemia cells in order to optimize this therapy and develop it further into a clinically successful treatment option.

Dr. Kipps is leading a project on the protein ROR1. He identified ROR1 in his laboratory investigations as an important protein, uniquely expressed by CLL cells. In adults, normal tissues do not have this protein. Since it is found in leukemia cells but not in normal tissue, it is an ideal vaccine candidate. The immune system is designed to recognize, respond, and react against foreign proteins, cells and microorganisms. Therefore, ROR1 is considered foreign and becomes an ideal target for the vaccine. Dr. Kipps will develop vaccines to stimulate the immune system to react against ROR1. When the R0R1 protein in the leukemia cells is attacked, the leukemia cells will also be eliminated. Dr. Kipps is also working on a DNA-based vaccine; he has modified the vaccine to optimize the vaccine's ability to stimulate a T-cell immune response.

Dr. Clemens Wendtner, University of Cologne, Germany, is looking to identify other proteins that may be leukemia-specific and can be used to monitor the anti-leukemia response and be developed into vaccines. His group has worked with a number of potentially important proteins in CLL, including fibromodulin, TOSO, CD23, CD229, and MDM2. Dr. Wendtner's group is also planning to participate in a clinical trial with the ISF35 vaccine in collaboration with Drs. Kipps and Januario Castro of UCSD. In this unique program, the vaccine is being used to sensitize the leukemia cells to chemotherapy. Patients will receive three doses of vaccine followed by chemotherapy as treatment for their disease. This trial will be for patients with resistant disease including those with 17p deletion. Dr. Wendtner will be working on the laboratory investigations for this trial.

The investigators in the Gene and Vaccine Therapy Alliance group are convinced that one of the most promising areas in CLL treatment research is the immune system's recognition of the leukemia and stimulation to eliminate the leukemia. : :

FIND OUT MORE ABOUT THE ALLIANCE AND OTHER PROJECTS WE ARE ACCELERATING AT

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CLL ALLIANCE

THE PROACTIVE CLL Patient

CLL research, treatments and prognostic markers have changed tremendously in the last ten years. Hopefully, in 2008, after hearing a diagnosis of CLL, it is not followed by the sentence, "But, if you are going to get cancer, this is the good cancer to get."

My husband has CLL. I am one of five founders of CLLForum (a communication channel run by people with CLL and their caregivers). There are many things that we tell the "newbies" about CLL. It is important to see a CLL specialist who will be aware of the new prognostic markers and the latest treatment or trial for CLL. It is also important to keep records of all your test results. Do not underestimate the value of finding support for your journey. And the most important thing is to give yourself time to wrap your head around the diagnosis of CLL. You will find your "new normal".

I would also like to suggest that you think about being a part of a trial. I lovingly refer to my husband as a "trial rat". At this point in the "World of CLL", there is no cure. There are some potential cures that involve transplant, but it is still considered a chronic, incurable cancer. The cure will come from clinical trials. Wouldn't it be great to be one of the first truly cured?

I applaud the CLL Global Research Foundation's efforts to accelerate CLL research and support promising trials and drug development. Dr. Keating's group is helping push the field of CLL research forward with a new initiative to bring together CLL experts from the U.S. and Europe. I look forward to hearing about the collaborative work that develops out of this unique Alliance. As members of the CLL community, whether patients, family members, physicians or researchers, we are all united with a common goal to better understand CLL and eventually eliminate it as threat to the life and health of patients and future generations of patients.

Jenny Lou Park. : :

Jenny Lou Park is the spouse of a CLL patient. She is an active proponent of CLL trials and patient education. She was pleased to contribute an article from a patient and family perspective.