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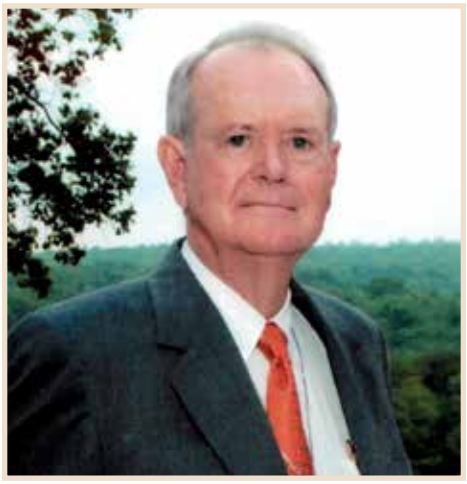
RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – A PROGRESS UPDATE

ISSUE 2-2013

A TRUE HERO: mack rankin



CLL research lost one its greatest advocates in August. We are saddened to share the passing of Byron McLean Rankin, Jr., better known as Mack. Mack dutifully served as Chairman of the Board of Directors of CLL Global since its inception. His shoes will certainly be difficult to fill; Mack provided incredible guidance and advice as CLL Global moved from a mere idea to a fully functioning, productive organization. He was the first person we called whenever a question would arise. Mack always provided his wise counsel and innovative perspective.

Mack never let his cancer diagnosis get the best of him. Instead, he concentrated on living life to the fullest. He spent endless hours supporting cancer research and helping those with a cancer diagnosis find the most appropriate care. He was a past Chairman and longtime member of the Board of Visitors at MD Anderson Cancer Center. Mack brought comfort and hope to those with cancer. He served as an example of the successful advancements in cancer treatment; he is recognized as one of the longest surviving patients in MD Anderson's history.

Mack was quite successful in the oil business. He co-founded McMoRan Oil, Inc. & McMoRan Exploration Company, later becoming Freeport-McMoRan. He stayed active in the business until his passing. He was quick to pass on his industry insights gained in the oil and mineral business. The company he founded now has more than 38,000 employees; yet he made participation in our relatively small organization an equally high priority.

Mack thrived in business but most importantly in his interaction with people. We will certainly miss his smile, words of advice, never-ending support and passion for University of Texas football. Mack was truly a gift to CLL Global. His support continues even in his passing, as his family has chosen CLL Global to be the beneficiary of memorial donations in his name. : :

Find out more about Mack by reading a tribute to his character and love of life as written by his wife Ashley with assistance from Rachel Landry.

inside this issue:

LANDSCAPE OF CLL

The CLL landscape has undergone a magnificent transformation from a barren desert to one bursting with growth of flowers and plants. Landscapes tend to thrive on the gifts of rain, and in our case the CLL terrain has benefitted from a downpour of new agents. In all cancers, patients, doctors and researchers are laboring to develop new agents, approaches and insights that lead to significant improvements in diagnosis and management of cancer. Sometimes, we labor without any success and other times, there are incremental discoveries like a slow, steady trickling rain over a few days. For CLL at the moment, the "breakthroughs" are like a thunderstorm soaking the landscape.

Some recent cancer breakthroughs have been driven by genetics and an improved understanding of the molecular changes that occur in the cancer cells compared to the normal cells. This is best illustrated by the development of imatinib (Gleevec) in chronic myeloid leukemia (CML). The discovery of a particular chromosome, Philadelphia chromosome, and subsequent understanding that it forms a new enzyme/protein which is not present in normal cells, led to the development of drugs to block this enzyme. Imatinib transformed CML from a life-threatening disease to one that can be controlled by an oral medication in the majority of patients. It has also led to improved outcome in some sarcomas of the gastrointestinal tract (GIST tumor) and acute lymphocytic leukemia (ALL) patients who happen to have the Philadelphia chromosome in their leukemic cells.

continue on page 4

protect yourself

AGAINST THE FLU

It is not too late. If you and your loved ones have not had an annual flu shot, there is still time. We are in the midst of the influenza (flu) season and the best way to protect yourself is by getting a flu shot. Family members can do their part by getting a shot; it is better for patients with CLL to avoid prolonged contact with people suffering from the flu.

Patients with CLL are already immunocompromised, giving them a somewhat higher risk for catching the flu. Immunocompromised patients need to worry not only about catching the flu but also the potential complications that arise from the flu such as pulmonary infections like pneumonia.

During flu season, there are lots of television ads telling you where to go and what kind of flu vaccine to get. One word of advice for patients with CLL is to get the flu shot as opposed to the nasal spray flu vaccine. The nasal spray flu vaccine is a live vaccine that carries a small risk of infection.

If a patient has advanced CLL or has received extensive prior chemotherapy, he or she may develop less immunity to the vaccine than healthy adults. Vaccines trigger antibody responses to provide protection; for this group of patients there may be a decreased antibody response to the vaccine. However, the flu vaccine can still provide some level of protection with minimal risk of side effects.

Researchers are working to improve the efficacy of the flu vaccine in CLL patients. Dr. Alessandra Ferrajoli and colleagues at MD Anderson Cancer Center are looking for ways to increase the level of immunoglobulins or proteins in the blood that may help to improve the immune system's function. Patients will receive the immune modulating agent lenalidomide before receiving the flu and pneumonia vaccines. Ferrajoli and colleagues will then evaluate whether administration of lenalidomide prior to the vaccines increases the level of immunoglogbulins and improves the protective effect of the vaccines in patients with CLL.

This study is just getting underway. For this flu season, the best advice is to get your flu shot and practice good personal hygiene. Do not underestimate the power of good hand-washing and use of hand sanitizers. It is always wise to consult your physician before being vaccinated, particularly if you have had severe reactions to prior flu vaccines or if you are allergic to chicken eggs. Here's to a healthy flu season for all of us. : :

INHIBITING BCR SIGNALING PATHWAYS

BCR signaling pathways are activated by the *B-cell receptor* located on the surface of all B-cells. There are various proteins involved in the signaling pathways but the two which have developed the greatest interest are Bruton's tyrosine kinase (BTK) enzyme and the PI3-kinase delta (PI3Kδ) enzyme. Drugs such as ibrutinib (BTK inhibitor) and idelalisib (PI3Kδ inhibitor) specifically block these enzymes. Both agents are oral and cause dramatic improvement in patients when given to treat their CLL.

Most of the clinical trials have been conducted in patients who have had previous treatments, and the majority of patients are over the age of 65. The most impressive changes to occur are very rapid decrease in size of lymph glands, and to a somewhat lesser extent the spleen, accompanied by an unusual rapid rise in the CLL cell count in the blood. This elevation can persist for 1 – 3 months and eventually resolves towards normal in most patients. As single agents, these drugs have a dramatic impact on the quality of life of patients and in the majority of individuals they are well tolerated. Very few patients come off ibrutinib because of side effects whereas a modest number of patients receiving idelalisib come off study for various reasons including diarrhea and lung infiltrates.

These drugs are now being studied in combination with a number of chemotherapeutic agents and monoclonal antibodies. The results of the early single agent studies are being compared and the combinations appear to have resulted in an increase in efficacy at this early stage of evaluation. Monoclonal antibodies of course do not damage the DNA of cells whereas chemotherapy combinations will have this element of risk. Neither of the agents has yet been demonstrated to have a significant effect on the immune system. ::

TARGETING SPECIFIC PROTEINS WITH BIOLOGICAL THERAPY

Monoclonal antibodies target specific proteins on the surface of the leukemia cell and play an important role in CLL treatment. Because of their specificity, monoclonal antibodies generate less damage to the cells outside their target. Rituximab which targets the CD20 protein was the initial monoclonal antibody shown to be active in CLL. The addition of rituximab to create the FCR regimen produced a significant survival advantage. Subsequent antibodies such as ofatumumab and obinutuzumab (also known as GA101) demonstrate superior activity to rituximab. Both of these new monoclonal antibodies have received "breakthrough" designation from the FDA. They attack the CD20 protein on the CLL cells at different sites. It is likely that rituximab will be replaced by one or both of these agents in CLL. A third generation of monoclonal antibodies targeting CD20 is in early stage of development.

New chemotherapy drugs continue to be developed. Bendamustine, an alkylating agent which works by damaging DNA, is now being investigated in CLL as a possible alternative to other chemotherapy programs. A German CLL Study Group clinical trial comparing FCR to bendamustine + rituximab is reaching maturity. Results of the early part of this study may be available at the American Society of Hematology Annual Meeting in December. ::

The landscape of treatment options has grown tremendously over the years.

1960's

Limited treatment options existed; CLL was treated like lymphoma since there were no CLL specific therapies.

1980's

The first new chemotherapy drug for CLL, fludarabine, came along.

1990's

Fludarabine combinations evolved. Fludarabine and cyclophosphamide (FC) were used for relapsed patients and as reduced conditioning for stem cell transplant.

2

The monoclonal antibody
This regimen dramatically
rate in the majority of

Other advancements: mo
was approved by the F
agent lenalidomide b
and the alkylating agen

DECREASING SURVIVAL PROTEINS

Excitement is also high for a group of drugs that aim to decrease the level of survival proteins called the BCL2 family. These proteins are increased in almost all patients with CLL and allow the CLL cells to live for approximately 100 days whereas normal B-lymphocytes have a survival of approximately 7 days. The decrease in the level of these BCL2 family proteins is associated with very rapid decreases in white cell count and shrinkage of lymph nodes.

An earlier version from this family of drugs, ABT-263, was associated with an expected but modest decrease in the platelet count due to its action on a molecule Bcl-XL; however, a subsequent version, ABT-199 which only targets Bcl-2 does not have this problem. ABT-199 is given orally and is usually associated with dramatic decreases in the CLL cell count and in lymph nodes. At this stage, it appears to be more effective than the inhibitors of the BCR signaling pathway (ibrutinib and idelalisib) in clearing cells from the bone marrow. Early laboratory studies suggest that ibrutinib and ABT-199 may be an effective combination that should be tested in future clinical trials. ABT-199 does not directly damage DNA, and the impact on the immune system is still to be evaluated. : :

HARNESSING THE IMMUNE SYSTEM

While the immune system is weakened in patients with CLL, studies of stem cell transplants particularly the "mini-transplants" have demonstrated that CLL cells are an excellent target for immune therapy. Mini-transplants or non-ablative stem cell transplants (NST) can now be administered to patients up to 75 years of age or even older which significantly widens the opportunity to do these transplants in older patients. They are certainly safer and easier than full ablative transplants but still can have significant complications.

The development of chimeric antigen receptor (CAR) therapy has led to the ability to educate patients' T-cells to attach to CLL cells when they are modified outside the body and returned to the patient. This process causes dissolving or "lysis" of the CLL cells. Unfortunately, the target CLL (CD19) is also found on normal B-cells so the normal B-cell section of the immune system is ablated (removed) and patients require continuing replacement of gammaglobulin. Scientists looked for a protein which is not present in the vast majority of normal cells but is present on CLL cells. ROR1 is such a protein and is now a target for the development of monoclonal antibodies and CARs against ROR1. These should not damage the normal B-cells. Small molecules which can be given orally to block the enzyme activity of the ROR1 protein are being developed. : :

2000's

rituximab was combined with FC. improved the complete remission CLL patients needing therapy.

noclonal antibody alemtuzumab FDA; the immune modulating egan to show activity in CLL, t bendamustine was approved.

2010's

In 2010, FDA approved the FCR regimen as the standard for patients. Many patients have demonstrated 10 years of continuing remission. There was tremendous progress over the first decade but currently is where we are seeing the next major transformation in CLL's landscape.

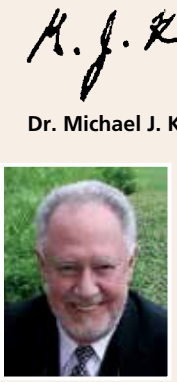
continued from page 1 (Landscape of CLL)

The CLL community has been waiting for a similar breakthrough; while there is not a proven "unique" enzyme in CLL, there are distinct signaling pathways in B-lymphocytes and increased survival proteins in almost all CLL patients.

On these pages, you will find out about potential treatments targeting these pathways and proteins as well as many other options that are helping to change the CLL landscape.

Many of these exciting developments have been supported by CLL Global grants. Thus, there is a storm of new agents peppering us. The challenge is to develop the best approach for each individual patient. Further exploration of the mechanisms driving these agents and how they can be most rationally combined is pivotal to improving the cure rate in patients with CLL. Nowadays it is much more fun for an investigator to be able to go "gardening" for new drug combinations than before when the landscape in the drug garden was bare.

We are making the transition from a rain deprived desert to the next generation which will include a rainforest of opportunities. The end of CLL as a threat to the health and survival of patients is very close. We need to accelerate the development of these approaches within the limits and constraints applied by regulatory agencies and the pharmaceutical companies. We must use our resources wisely and well for the benefit of all patients with CLL and to develop available treatments which are accessible by patients regardless of their societal or economic class. Help us to continue transforming the treatment landscape for future CLL patients. : :



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.

MEET THE LATEST grant recipients

This issue of *Momentum* is filled with an array of new drugs under development for CLL. A goal for each new therapy is to improve remission and survival rates. With existing treatments patients may relapse or develop resistance to re-treatment. The New Drug Development working group of the CLL Global Alliance is working on developing therapies that target resistance mechanisms of the disease. CLL Global recently awarded $850,000 in total to four members of the working group pursuing therapeutic strategies that selectively kill malignant CLL cells and overcome drug resistance. Below, we introduce you to the four investigators and the key aims of the research.

Varsha Gandhi, Ph.D.
MD Anderson Cancer Center

NOVEL STRATEGIES FOR CLL TREATMENT

Dr. Gandhi and colleagues are looking at three different strategies for new treatments. Traditionally used agents such as cyclophosphamide and bendamustine (which are examples of alkylating agents that damage DNA) result in cytotoxicity and damage to normal cells. Dr. Gandhi is working to develop new treatments that will selectively kill CLL cells. CLL cells have high levels of reactive oxygen species (ROS) (which are molecules containing oxygen); this project aims to create alkylating agents that are activated only with high ROS. Dr. Gandhi's team is collaborating with a chemist at the University of Wisconsin who has created novel alkylating agents that are selectively activated by high ROS levels in CLL cells. Dr. Gandhi plans to test activity of these agents in CLL as well as in normal lymphocytes. They will test levels of ROS and activity of newly synthesized compounds. She will also test if these agents induce DNA damage, which is a primary mechanism of action of an alkylating agent.

The second approach is looking at a specific kinase or enzyme that helps in cell survival. PI3kinase is found at high levels in CLL cells in two different forms, delta and gamma. Gilead's experimental agent, idelalisib, targets only the delta form and Infinity's compound, IPI-145, hits both delta and gamma. Dr. Gandhi is using CLL lymphocytes from the blood of patients to check if inhibiting both forms of the enzyme will result in increased cytotoxicity. They will determine if both forms are present in cells. In addition, they will test if incubating cells with IPI-145 results in cell death and if normal lymphocytes are spared.

Dr.Gandhi's final approach looks at a different enzyme called caspase which must be activated for CLL cells to undergo cell death. They are studying a new compound, L14R8, which directly activates this enzyme. The group is using CLL lymphocytes obtained from patients' peripheral blood to test if L14R8 activates the enzyme. They will determine if this treatment results in CLL cell death and will compare expression levels of this caspase in its inactive form in CLL cells and normal lymphocytes. : :

Deepa Sampath, Ph.D.
Ohio State University

MECHANISM BASED COMBINATIONS FOR THE THERAPY OF CLL

CLL is characterized by a slow accumulation of cancer cells; however the CLL cells have an enhanced ability to survive. The ability to survive is caused by several factors including high levels of expression of DNA repair proteins and the activation of a protein (Bruton's tyrosine kinase or BTK). Dr. Sampath is looking at strategies to decrease expression of DNA repair proteins and BTK to result in the death of CLL cells. The project focuses on how a novel class of agents, histone deacetylase inhibitors (HDACi), can be used in combinations to eradicate CLL cells. HDACi agents have already shown promise in certain lymphomas.

In normal cells, genes called microRNAs keep the levels of DNA repair proteins and BTK from becoming excessively high. However, in CLL the production of the microRNAs that control DNA repair proteins and BTK is shut down and the DNA repair proteins and BTK increase in number. Without microRNA production, CLL cells can repair DNA damage caused by chemoimmuno-therapy, making chemoimmunotherapy less effective. Recently, the BTK inhibitor, ibrutinib, has been very successful in CLL. However, some patients develop resistance to ibrutinib. Therefore, alternative methods to decrease BTK protein will become important in order to treat CLL

Dr. Sampath's project tries to move beyond chemoimmunotherapy treatment that damages DNA. She hypothesizes that when CLL cells are exposed to the HDACi agents panobinostat or abexinostat, they will block the action of the HDACs which allows the microRNAs to function. Once the microRNAs function properly they will reduce the levels of DNA repair proteins as well as the survival molecule BTK. These actions of the HDACi will make the CLL cells more prone to death when combined with chemoimmunotherpy (because they can no longer repair DNA damage) or ibrutinib (because it reduces the absolute levels of BTK). These data will help in the development of HDACi's as a drug for the treatment of CLL. Sampath's group will obtain blood from CLL patients and healthy donors, as permitted under a protocol approved by the Institutional Review Board (IRB). : :

Bill Plunkett, Ph.D.
MD Anderson Cancer Center

STRATEGIES TO TARGET THE PATHOPHYSIOLOGY OF CLL

This project is focused on the characteristics of CLL that contribute to resistance to current therapies and has three main aims. First, a percentage of patients have a small portion of genetic material (chromosome 11) deleted from the CLL cells. This region contains the ATM gene which instructs cells to repair a type of DNA damage. Dr. Plunkett's group is developing a treatment for this subgroup of CLL patients with a new drug, sapacitabine. Sapacitabine causes specific DNA damage. They expect that CLL cells lacking the repair mechanism will respond favorably, thus controlling the CLL. The clinical study of sapacitabine is ongoing. Dr. Plunkett's lab is looking at the function of the ATM gene in sapacitabine-treated patients.

Second, Plunkett will use new agents to interfere with the synthesis of proteins that are continuously required for CLL viability. Normal cells do not require these proteins. The proteins are normally destroyed in a rapid fashion; therefore the CLL cells must make them continually in order to survive. The team proposes that brief inhibition of the synthesis of these proteins will result in a decrease in their levels and selectively cause CLL cells to die. Their earlier studies show that this inhibition causes death of CLL cells but not of normal cells.

Finally, a newly discovered deletion in CLL genetic material (SF3B1 gene) includes the instructions for how to make proteins. The deletion of SF3B1 gene is associated with poor response to therapies, but the mechanism by which this affects clinical outcome is not known. Plunkett's preliminary experiments indicate that the loss of the SF3B1 gene and corresponding SF3B1 proteins affects other proteins that keep CLL cells alive. The group will first explore this possibility in animal models and if the results are positive, they will design investigations in fresh CLL samples that have this loss of genetic material. ::

Peng Huang, M.D., Ph.D.
MD Anderson Cancer Center

NOVEL AGENTS TO TARGET METABOLIC ALTERATIONS IN CLL AND OVERCOME DRUG RESISTANCE

Dr. Huang's project aims to overcome CLL drug resistance occurring within the tissue environment. The group's recent work suggests that CLL cells have certain changes in their metabolic pathways which impact energy generation and antioxidant production. They have also discovered that normal tissue cells play a key role in protecting leukemia cells by helping them to maintain proper metabolism and antioxidant capacity. This results in leukemia cell survival and drug resistance.

Based on these new findings, Dr. Huang's group is now targeting the altered metabolic pathways in CLL cells. The group hypothesizes that blocking their interaction with tissue cells may be an effective strategy to eliminate the leukemia cells within the body. They have identified several promising compounds that kill CLL cells by inhibiting these metabolic pathways.

In this research project, they will investigate the ability of these compounds to kill CLL cells in the tissue microenvironment. The team will try to understand the underlying mechanisms of action for these agents and hope to develop drug combination strategies to improve therapeutic activity and overcome drug resistance. The group will use CLL mouse models and primary leukemia cells from CLL patients to test the therapeutic activity and validate drug targets. They will also conduct laboratory studies to obtain information on the safety profiles of these compounds. Such information is critical for potential clinical trials of these compounds. The successful completion of this research project could lead to the development of a new class of agents capable of effectively killing CLL cells and overcoming drug resistance in tissue environment. ::

CAN WE START USING **CURE** with CLL?

The CLL community has been buzzing around using the word cure over the last few months. Patients are asking could it be true. Physicians emphasize that the discussion is limited to a particular portion of patients. All of the comments resulted from data presented at the biennial International Workshop on CLL (iwCLL) held in September in Cologne, Germany.

Presentations from the MD Anderson Cancer Center and German CLL Study Group both showed long-term remission data using fludarabine, cyclophosphamide and rituximab (FCR). In independent studies, both groups observed that patients with an IgHV mutation had a longer-term progression free survival than unmutated patients. MD Anderson data showed 60% of IgHV-mutated patients to be in remission or progression free beyond nine years. The German data showed more than 50% of IgHV-mutated patients to be progression free beyond eight years.

This data suggests that if patients are mutated and have made it more than eight or nine years without a relapse, then it may be time to start using the word cure. This is the first time that the word cure has been discussed with a CLL chemoimmunotherapy regimen .

The research community has known for a while that the mutation status of the IgHV gene is an important prognostic factor. IgHV genes are found in the DNA of lymphocytes and are responsible for producing antibodies. A mutated IgHV gene is a good prognostic factor. The more mutated IgHV genes are, the more mature the genes are, making them more capable of protecting the body. The FCR data presented at iwCLL further confirms IgHV mutation status as a useful prognostic factor.

However, FCR is not the ideal regimen for all patients, particularly 17p del patients. Therefore, work continues to find effective treatments for all subgroups. Even for patients that do well under FCR, such as the mutated group or patients with trisomy 12, the research community is looking at whether FCR can be improved. FCR is generally given for six months. Can fewer cycles of the chemotherapy be given to still produce the positive outcomes but minimize the subsequent events and toxicity associated with chemotherapy? Work will continue until the word cure can be used for all subgroups of CLL patients. ::