Year 2: Still On Target to Beat AML

In 2013, LLS began a three-year collaboration of academic, industry, and technology partners to accelerate the discovery of new treatments for patients with acute myeloid leukemia (AML). The multi-institutional initiative is known as Harry T. Mangurian Jr. Foundation–Beat AML. It is led by top scientists at the Knight Cancer Institute at Oregon Health & Science University (OHSU) and takes a next-generation approach to personalizing therapies.

The goals are to collect and study patient samples, create a profile of the genetic and molecular abnormalities that drive the disease and simultaneously test targeted agents and drug combinations. The aim is to move from relatively uniform and non-specific treatments to having genetic analysis guide therapeutic choices.

Patient Samples
As of August 2015, 400 unique AML patient samples have been collected and analyzed from five participating centers. The University of Colorado - Denver was recently added and joins the Knight Cancer Institute, Stanford University, University of Texas Southwestern Medical Center, and Huntsman Cancer Institute at University of Utah. Partnerships with up to three other centers are in process to further boost sample accrual. The volumes of samples and the level of detail that is collected are enabling the Beat AML team to build an extensive biological map of the disease.

Targeted Therapies
Beat AML established seven biotech/pharma partnerships that include 14 proprietary, clinical-stage drugs. Two more industry partners are in advanced discussions to contribute several more proprietary drugs.

Functional assays are being used to identify pairs of drugs that might work better than individual drugs. Combination testing has been completed for 150 patient specimens to date. Data from this work uncovered a number of drug combinations that work effectively together to block AML cell growth.

At least ten abstracts from Beat AML research have been submitted for presentation at the December 2015 annual meeting of the American Society of Hematology. In that setting, specifics of the previously confidential research will be shared with a wider audience.
Genomics and Bioinformatics

Genome-sequencing technologies have dramatically increased the amount of genetic information that can be collected from a patient's tumor. With the drug-screening pipeline and industry partners in place, the focus has turned to the genetic sequencing and analysis of the large amounts of generated data. Thus far, genomic analyses have been performed on more than 250 patient samples.

Preliminary analyses identified recurrent mutations including a newly discovered one found by LLS-funded researcher, Jeffrey Tyner, PhD at OHSU. Dr. Tyner identified a mutation in the anaplastic lymphoma kinase (ALK) gene, the first time this was found in an AML patient. This finding suggests that AML patients with ALK mutations could benefit from treatment with ALK-targeting drugs, two of which are already FDA approved for forms of lung cancer.

The Beat AML team is working to uncover more genetic alterations, correlating these with drug response and immune profiling, and identifying signaling pathways for further study. More than 20 pathways and potential new targets have been identified so far for follow-up studies. This information about AML biology will help identify biomarkers to predict individual patients’ responses to treatments, uncover the mechanisms by which experimental drugs work, and even suggest new therapeutic targets.

Beat AML is continuing to work with technology partners to improve the capacity to analyze large amounts of data and share it with others. Intel and OHSU launched the Collaborative Cancer Cloud, a precision medicine analytics platform for which Beat AML serves as a pilot data set. This partnership aims to accelerate personalized therapy into a 24-hour time frame and improve data sharing and cloud computing among widely dispersed collaborators.

Clinical Trials

Beat AML has made progress towards incorporating drug sensitivity, genomic sequencing, and patient medical data into clinical trials. A Phase 2 trial for patients with relapsed/refractory AML is enrolling patients and using the drug sensitivity screen developed by the Beat AML team to select an optimal targeted therapy for each patient from a five-drug panel. Genetic sequencing data will identify potential biomarkers for drug sensitivity. The trial’s concept and design led to a key component of Beat AML: a Phase 1b trial using the drug-sensitivity screen to identify optimal targeted therapies to be combined with chemotherapy for newly diagnosed AML patients. This trial, working its way toward regulatory approval for a winter 2015 start, will use deep-sequencing methodologies to monitor the remaining disease in patients and gauge the effect of the agent on disease progression.

Both trials use drugs that are FDA approved for other cancers but are not standard therapy for AML. This allows for faster approval to hasten the pace of adding new treatments to the arsenal for AML patients. Patient samples will feed back into the functional genomics platform to help identify new biomarkers and responsive subgroups of patients. Most important, the trials provide clinical validation for the concepts of personalized medicine and combinations therapies advanced by Beat AML research.

Additional drugs will be incorporated into the trials after identification of recurrent sensitivity to these drugs in the larger Beat AML drug panel. Trial protocols are also being developed to test early-stage novel drugs (pre-FDA approval) from Beat AML industry partners.

Coming Soon

Findings from these exploratory trials and Beat AML preclinical research will feed into a parallel large-scale clinical trial, spearheaded by LLS, to bring genomics-based personalized medicine for AML into the mainstream. A master trial will serve as the umbrella under which several trials will each test a different biomarker. With multiple sites, the trial will enable AML patients possessing specific genomic biomarkers to have access to tailored targeted drugs early in their treatment, prior to standard chemotherapy. It is expected that using drugs that are highly effective for a specific, genetically unique patient population will produce better outcomes.
Small Cancer Group
Gets Large Collaboration

T-cell lymphomas comprise about 10 percent of non-Hodgkin lymphomas in Western countries. In a poorly understood subset known as peripheral T-cell lymphomas (PTCLs), good therapies are non-existent. PTCL patients are treated with drugs used in B-cell lymphomas and they represent a disproportionately large fraction of lymphoma patients who succumb to their disease.

Numerous roadblocks have caused PTCL advances to lag behind other lymphomas. First, they are difficult to classify, with 30 percent categorized as “not otherwise specified,” far more than any other leukemia or lymphoma. And even in known subtypes, small numbers make it difficult to enroll sufficient patients in clinical trials. And finally, there is an almost complete absence of model systems.

Unlike commercial enterprises that seek therapies for large markets, LLS invests in unmet needs and recently approved a $6.25 million collaboration to improve treatment for PTCL patients. It is led by David Weinstock, MD, at the Dana Farber/Brigham and Women’s Hospital. Together with scientists at Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, Stanford University and the University of Nebraska, the group will test drugs already developed in other cancers that have the same molecular drivers found in PTCLs.

Three alterations have been identified in some of the known PTCL subtypes, and these defined pathways can be modeled and targeted. Giorgio Ihghirami, MD, at Weill Cornell is testing an inhibitor of the mutant JAK/STAT pathway; Craig Thompson, MD, at Memorial Sloan Kettering is testing an inhibitor of the mutant protein IDH2 and Dr. Weinstock is testing PI3K signaling inhibitors. The team also has patient-derived tumor xenografts that are valuable as mouse models of human disease. These are more useful than mouse models using non-patient laboratory established cells that can produce a positive tumor response in mice but might not translate over when a study is implemented in humans.

Armed with model systems and multiple inhibitors in clinical development at the collaborating institutions, testing can advance quickly with adequate trial enrollment through the multicenter consortium. This will offer the first opportunity to stratify PTCL patients based on validated biomarkers, identify mechanisms of response and resistance, and advance next-generation trials for patients who currently have few good options.

Starving CML Stem Cells to Overcome Therapy Resistance

Chronic myeloid leukemia (CML) occurs when parts of two chromosomes switch places to produce the “Philadelphia chromosome” and the cancer-causing BCR-ABL gene. Current therapies, known as tyrosine kinase inhibitors (TKIs), include imatinib (Gleevec”) and subsequent, more potent agents. These are highly effective in chronic phase CML patients and the five-year survival rate is more than 90 percent. However, the treatments are not curative and if discontinued, the disease generally recurs due to a small number of CML stem cells that resist therapy.

Xiaoyan Jiang, MD, PhD, at the British Columbia Cancer Agency is targeting the surviving cells. Funded by LLS of Canada, she is investigating autophagy a process that enables cells to recycle proteins and release nutrients to counteract cell death.

Dr. Jiang hypothesizes that CML stem cells harbor a unique autophagy gene known as ATG4B that could predict patient response to TKI therapy and serve as a new therapeutic target. Using a technique known as knockdown, ATG4B expression can be reduced by genetic modification and thus block the fuel needed by the stem cells to survive.

Dr. Jiang and colleagues have identified several ATG4B inhibitors and are testing whether the combination of TKIs and ATG4B inhibitors will inhibit the growth of BCR-ABL stem cells and block leukemia development. If successful, this can present a new approach to overcome TKI resistance in CML.
In August, the FDA approved an investigational new drug application, a key step in allowing a clinical trial of a potential new therapy for people with relapsed or refractory non-Hodgkin lymphoma. The approval was a significant milestone in a partnership between LLS and Valor Biotherapeutics.

Through its Therapy Acceleration Program, LLS committed to co-fund the pre-clinical development and clinical grade manufacturing of IGN002, a new class of genetically engineered biotherapeutics. For the past two years, staff at LLS, Valor and ImmunGene (a joint venture partner with Valor) collaborated to complete the pre-clinical development and manufacturing of IGN002 that were needed to pursue the FDA approval.

IGN002 is genetically engineered by fusing an antibody with interferon, a protein that plays a critical role in regulating the immune system. Together, they form a potent agent that can be safer and less toxic while maximizing targeted anti-tumor effects. IGN002 has the potential to improve treatment outcomes for certain non-Hodgkin lymphoma patients.

This potential new therapy originated in an LLS translational research grant to Sherie Morrison, PhD, at UCLA. She attached the anti-cancer agent interferon-alpha (IFNα) to the antibody drug Rituxan® that targets the protein CD20 present on all B cells. This novel fused agent leverages the specificity of antibodies with the potent killing effects of interferon, while avoiding interferon’s toxicity. Recognizing the value of Dr. Morrison’s work, LLS made the additional investment to advance the anti-CD20/IFNα fusion drug as a treatment for B-NHL patients with CD20+ that become non-responsive or relapse soon after Rituxan therapy. Preclinical studies have shown that IGN002 is more effective and safer than either IFNα or anti-CD20 antibodies, even when used in combination. With the recent FDA approval, a Phase 1 clinical trial will begin.