

HIGHLIGHTS

Fall 2014

FOR DONORS



The Leukemia & Lymphoma Society (LLS) exists to find cures and ensure access to treatments for all blood cancer patients. Because there are no means of preventing or screening for most blood cancers, we focus on finding cures. LLS values your generosity because progress happens when smart money and smart research meet.

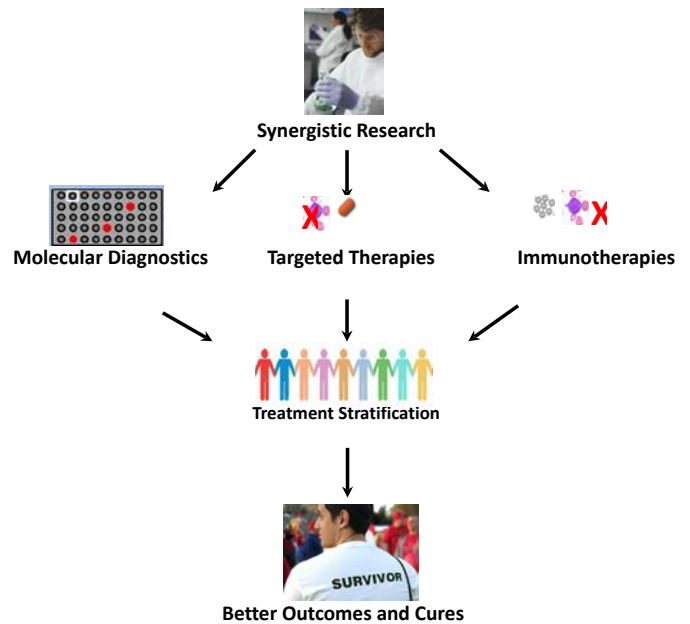
Year 1: On Target to Beat AML

Last fall, LLS announced a pioneering, three-year collaboration among scientific researchers, pharmaceutical companies and technology enterprises to move “precision medicine” toward reality for people with acute myeloid leukemia (AML). The Harry T. Mangurian, Jr. Foundation - Beat AML project is led by Brian Druker, MD, of the Knight Cancer Institute at Oregon Health & Science University. Dr. Druker previously introduced targeted treatment with Gleevec for chronic myeloid leukemia patients.

AML is complex and difficult to treat. It includes a great diversity of gene mutations and molecular abnormalities, especially in early vs. late forms and at relapse vs. presentation. Yet the therapies are relatively uniform and non-specific. As a result, patients either do not respond or relapse. Because the disease is aggressive, effective targeted therapies need to be quickly identified and used.

Precise goals of this large-scale project to beat AML are to collect and study samples from 900 patients, create a profile of the genetic and molecular abnormalities that drive the disease and simultaneously test a wide variety of novel targeted agents and drug combinations. By understanding the relationship between the functional effects of certain drugs and the genetic defects, the aim is to get the right drug to patients at the right time. Ultimately, genetic analysis will guide therapeutic choices for patients.

In its initial year, the collaboration achieved all Year 1 milestones on several fronts:



Patient Samples

As of September, nearly 200 unique AML patient samples have been collected from the four partnering academic centers, Knight Cancer Institute, Stanford University, UT Southwestern Medical Center, and Huntsman Cancer Institute at University of Utah. Additional partners are expected in the next 3-4 months to boost sample accrual.

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Year One On Target to Beat AML

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Molecular Diagnostics & Analysis

Technology partner Illumina, which provided whole-genome sequencing expertise, was removed when a switch was made to perform whole-exome sequencing at the Knight Cancer Institute. The exome is the portion of the human genome that contains sequences of DNA that direct the body to make essential proteins. These regions are called exons where most DNA sequencing errors that lead to genetic disorders are found. Compared to genome sequencing, the exome sequencing is more time- and cost-effective, requires less DNA per sample, and is better suited to identifying insertion/deletion mutations.

Intel worked with the bioinformatics team to accelerate the computational analysis of the mutation data collected from the patient samples. BD2K (Big Data to Knowledge) was added at UC/Santa Cruz to help provide statistical power needed to understand the complex relationships between genotype (the genetic code in cells) and phenotype (the visible or expressed trait, such as hair color).

Targeted Therapies

In September, Aptose Biosciences was added as a new biotechnology partner. Its lead anticancer therapeutic, APTO-253, is a clinical stage small molecule that induces cell death in AML lines by a novel mechanism and synergizes with other conventional therapies. It will be profiled extensively against primary cells from the patient samples. Aptose is also developing a companion diagnostic to select patients with positive genetic prognostic factors to APTO-253, offering the potential for a personal medicine in AML.

Treatment Stratification

AMPLab at UC/Berkeley was recruited to develop an algorithm that uses clinical, genomic and functional data to predict optimal combination therapies for a specific patient. It is hoped that the algorithm can be tested in a clinical trial.

Better Outcomes

Finally, progress has been made toward the ultimate goal: to improve outcomes for AML patients. A phase II clinical trial is open for patients with relapsed/refractory AML. Patients will be included in the trial if they show sensitivity to one or more of five therapies using an FDA-approved drug-sensitivity screen. Genetic sequencing data will be collected from patients to identify potential biomarkers for drug sensitivity. A second trial, which aims for a late 2015 start, will use the drug-sensitivity screen to identify optimal targeted therapies, in combination with chemotherapy, for patients with newly diagnosed AML.

Commercial Collaborations to Intercept Progression to Advanced Blood Cancers

LLS has a new partner in the Therapy Acceleration Program (TAP) through which we forge collaborations with commercial enterprises to help bring therapies to patients faster. The TAP partner is OncoPep, a biotechnology company that is developing an experimental cancer vaccine (PVX-410) that contains four proprietary peptides designed to target tumor antigens found on the surface of multiple myeloma cells. The experimental therapy was granted orphan drug designation from the FDA in 2013.

A \$690,000 commitment from LLS will support clinical development of PVX-410 that is being studied in patients with smoldering multiple myeloma. This is the name for the asymptomatic stage of multiple myeloma that has a high risk of progressing to full-blown multiple myeloma. PVX-410 has the potential to be a future therapeutic option for patients whose current treatment regime is routine monitoring for progression through watchful waiting.

To date, 12 patients have been treated with the vaccine in a Phase 1/2 clinical trial that is testing safety and tolerability of PVX-410 alone and in combination with lenalidomide, an agent that might complement the mechanism of action of PVX-410. The trial is open in three sites in Boston and one each in Atlanta and Houston. If this therapy advances, it would become the only clinical stage immunotherapy for smoldering multiple myeloma patients and might prevent them from progressing to active disease.

In a separate program, LLS is jointly sponsoring a new initiative with Janssen Research and Development, a Johnson & Johnson company, to further understand the progression of myeloid malignancies from a chronic, early stage disorder such as myelodysplastic syndromes or myeloproliferative neoplasms to advanced myeloid blood cancers. A joint Request for Proposals for the Transforming Cures Initiative encourages research to identify what drives progression to leukemia, including a better understanding of the roles of the immune system and microenvironment in enabling disease progression, and to develop predictive models and treatment strategies including vaccines, nutraceuticals and drugs.

FDA Hastens Approvals with Breakthrough Therapy Designations

In July 2014 the U.S. Food and Drug Administration designated CTL019 as a *Breakthrough Therapy*. This promising immunotherapy, also known as chimeric antigen receptor (CAR) therapy, genetically engineers patients' immune T cells and reintroduces them into the body to kill cancer cells. The pioneering work is led by Carl June, MD, at University of Pennsylvania. Over the last 16 years LLS has committed \$21 million to Dr. June and his team to advance this therapy.

Breakthrough Therapy designation was created by the FDA in 2012 to expedite the development and review of drugs for serious or life-threatening conditions. To be put on this path, preliminary clinical evidence must demonstrate that the drug represents a substantial improvement over available therapy. The designation gives an “all hands on deck” approach at FDA with more intensive guidance on a drug development program, an organizational commitment by senior managers in all relevant divisions, and eligibility for expedited review. The first drug to receive the designation was obinutuzumab, now used in combination with chlorambucil for previously untreated patients with chronic lymphocytic leukemia (CLL). Ibrutinib, recently approved for patients with CLL and mantle cell lymphoma (MCL) and supported in laboratory work and clinical trials by LLS, was another of the earliest products with this special designation. In fact, 12 of 51 designations to date have been for blood cancers.

Dr. June's CTL019 therapy is the first genetically-engineered cancer immunotherapy to receive the breakthrough designation and so far nearly 90 percent of acute lymphoblastic leukemia patients who were not responding to conventional therapies went into complete remission after receiving the engineered T cells.

The Human Side of Clinical Trials

Like any healthy 49-year-old, Doug Olson didn't see cancer coming. But in 1996 he was diagnosed with chronic lymphocytic leukemia, CLL. It was six years of watch-and-wait before active treatment was needed. After a five year remission, a second round of therapy produced a partial remission that lasted less than two years. By September 2010 he was resistant to chemotherapy and his oncologist, David Porter, MD at the University of Pennsylvania, recommended a bone marrow transplant. Doug, a PhD scientist, knew this procedure would have a 50-50 chance of success. As he considered the risk, Dr. Porter came back to Doug with another option – a clinical trial using an experimental therapy of engineered T cells that had been effective so far only in mice. Cells would be taken from Doug and re-programmed to become leukemia-specific serial killers, each capable of killing 1,000 leukemia cells. The engineered cells would self replicate, working like a vaccine.

An optimist who refused to be a cancer victim, Doug enrolled in the trial as patient 002. Four years later, he has no leukemia and plenty of active CAR cells.

LLS Aligns Players in the Innovation Ecosystem



The puzzle from discovery to new patient therapies is long (10-15 years), risky (one approval for every 5,000-10,000 compounds) and expensive (\$1 billion+). LLS is highly engaged throughout the process, investing in science and aligning key players:

- Funding research across the continuum from discovery to clinical trials
- Partnering with commercial enterprises to develop new therapies
- Linking patients with clinical trials
- Speeding FDA approvals
- Helping patients access new treatments

As a demonstration, as LLS-funded researchers were running clinical trials with ibrutinib, our staff in Washington, D.C. and a network of advocates nationwide were pushing FDA to hasten the approval of new treatments in blood cancers. Simultaneously, LLS was securing philanthropic funding to help patients afford costly new treatments. When FDA signaled new approvals this past spring, LLS was ready to offer co-payment assistance in an expanded program that now includes patients with mantle cell lymphoma.

Improving the Quality of Survivorship in Young Patients

For children under age 15 who are diagnosed with leukemia or lymphoma, long-term survival is an expected outcome. Their survival rates exceed 90 percent in acute lymphoblastic leukemia and 98 percent in Hodgkin lymphoma. The harsh curative treatments, however, can produce long-term and late side effects that reduce the quality of life.

Among the noted late effects is congestive heart failure, an inability to pump enough blood to meet the body's needs. A class of chemotherapy drugs known as anthracyclines, which are used to treat pediatric blood cancers, increases the risk of heart problems. An estimated 1 in 10 children treated with high-dose anthracyclines will develop heart failure and of these, half will die within five years. As more and more children survive pediatric blood cancers, LLS is determined to improve the quality of their survivorship.

Among the LLS grants focused on survivorship is one to Dr. Saro Armenian, a pediatric hematologist/oncologist at City of Hope in California. Dr. Armenian is running a clinical trial to minimize the risk of heart failure in young patients exposed to high-dose anthracyclines. In a randomized phase II trial at sites in California, Tennessee and Michigan, he is using carvedilol, a low dose blood pressure medication. Studies in adult non-cancer populations indicate that carvedilol may help prevent the onset of congestive heart failure.

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Of the 67 patients enrolled in the trial, some receive carvedilol and others a placebo. Adherence to the twice-daily pill is high at 90 percent and no adverse reactions have been reported in either arm of the trial.

This study provides feasibility for a larger scale trial to include other cancer survivors exposed to high-dose anthracyclines in childhood (bone tumors and sarcoma) or in adults (leukemia, lymphoma and breast cancer). It will be needed to evaluate whether adding a prophylactic drug can help ensure that survivors live long and healthy lives after completing treatment.

Dr. Armenian's career was shaped by personal experience. As a teen, he served as a bone marrow donor to his sister who had leukemia.

We've included LLS in our estate plans **because...**

"... it leverages the value of our bequests beyond what a gift would do for a single researcher or institution. As a retired clinician and researcher in adult leukemias, I've worked with incredible scientists all over and want to support great science and novel ideas wherever they're found. I've also seen The Leukemia & Lymphoma Society from many perspectives – a funded researcher, board member, medical advisor, and grant reviewer – and continue to be impressed by the organization's focus on its mission." —*Judith E. Karp, MD and her husband, Stanley Freedman*



With a gift in your will or a beneficiary designation in your retirement plan, you can support life-saving research too. For details, contact Richard Schneyer at 1.888.773.9958 or richard.schneyer@LLS.org.