HIGHLIGHTS
FOR DONORS

Summer 2015

someday is today

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

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.

Rebalancing the Immune System to Control Graft vs. Host Disease

A transplant of donor hematopoietic stem cells (blood-forming cells in the bone marrow) can be a curative option in advanced or aggressive blood cancers. In this procedure, stem cells from the bone marrow, blood or umbilical cord blood donor are used to rebuild the recipient immune system and enable immunologic killing of their cancer cells.

However, the new immune cells (the graft) can also identify normal cells in the recipient (the host) as foreign and attack them. This Graft-versus-Host Disease (GvHD) can develop within a few weeks (acute) or later (chronic) and affects more than half of long-term transplant survivors.

LLS-funded researcher John Koreth, MD, PhD, at Dana-Farber Cancer Institute in Boston, seeks to alleviate GvHD using interleukin-2 (IL-2) to restore immune system balance.

In the healthy immune system, effector T cells defend the body in an immune response and regulatory T cells (Tregs) restrain the response to prevent inappropriate or excessive immune reactions. Researchers have recognized that the naturally occurring Tregs might be used to control chronic GvHD and that patients with chronic GvHD are deficient in reconstituting Tregs. Efforts to control GvHD with Treg cells that were expanded in the laboratory have shown efficacy in lab animals, but have been difficult to implement in the clinic. Alternative approaches to enhance Tregs in a patient's own body without ex-vivo cell manipulation are needed.

Dr. Koreth and his colleagues theorized that low doses of a natural substance, IL-2, could preferentially activate Tregs and might help control excessive immune reactions underlying chronic GvHD. In a Phase 1 trial of patients with refractory chronic GvHD, he documented that low doses of IL-2 considerably enhanced Treg cells, not just by inducing proliferation of existing cells in the blood, but also by enhancing their natural production from the thymus gland. In the trial, more than half the chronic GvHD patients improved with daily, low-dose injections of IL-2. Dr. Koreth is now exploring whether IL-2 can be effective if used earlier in the course of chronic GvHD. In a follow up Phase 2 trial, early results strongly support the earlier phase data.

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These findings that immune system overactivation can be controlled by enhancing natural Treg cells rather than using additional immune suppression medications, is relevant not just to GvHD, but to other disorders of impaired immune tolerance, including autoimmune disorders and solid organ transplantation.

Rare Lymphoma Requires Continued Investment

When the U.S. Food and Drug Administration approved ibrutinib earlier this year for new and relapsed cases of Waldenström's Macroglobulinemia (WM), it marked the first therapy approval specifically for WM patients. There has been no standard of care for this rare form of lymphoma and while most patients respond to combinations of chemotherapy, disease relapse has been the norm.

Ibrutinib, which was previously approved for patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), inhibits the Bruton's tyrosine kinase (BTK) enzyme that promotes WM growth. LLS supported the research and clinical trials of BTK inhibitors.

LLS has actively funded WM research over the years and convened a two-day gathering of experts in 2009 to identify obstacles to progress. When they concluded that disease-specific cell lines were needed to investigate the cancer's biology and test new therapies, LLS partnered with the International Waldenström's Macroglobulinemia Foundation (IWMF) to fund investigators to develop the needed cell lines. In May 2015, LLS partnered again with IWMF to update the road map and determine where to invest new resources for optimal benefit.

In a current LLS-funded study, Steven Treon, MD, PhD, at Dana-Farber Cancer Institute discovered two signaling pathway mutations. One of them, MYD88, is found in 90 percent of WM patients. This mutation activates BTK and IRAK1 proteins that drive WM growth and survival. While ibrutinib inhibits BTK, the other protein remains active. Dr. Treon combined ibrutinib with an IRAK1 blocker in the lab and saw increased WM cell death. He is now testing single and combination therapies in a mouse model.

Through its Therapy Acceleration Program, LLS is looking to advance the development of an antibody therapeutic in a Phase 2 clinical trial of patients with refractory WM. Along with biotechnology partner arGEN-X, the trial is testing a highly potent, anti-CD70 antibody. CD70s are overexpressed in 100 percent of the WM patient samples tested.

Investments in rare diseases are not restricted to the lab and to the clinic because new therapies are ineffective if patients don't have ready access. To help with the cost of treatment, LLS expanded its co-pay assistance program with a new funding gate for WM patients to help pay for insurance premiums and meet co-payment obligations. Qualified patients are eligible for assistance up to $5,000.

LLS Bridges Gap Between Academia and Industry

A promising University of Michigan research project led by Jolanta Grembecka, PhD, to develop new treatments for patients with a rare and lethal subtype of leukemia received a significant boost from a licensing agreement with biotechnology company Kura Oncology. Supported by more than $8 million in LLS funding since 2009, this is an excellent example of how the LLS Therapy Acceleration Program (TAP) identifies promising academic projects and chaperones them toward potential drug development.

Dr. Grembecka has focused on leukemia associated with abnormalities in the mixed lineage leukemia (MLL) gene. In cancers, the abnormal rearrangement of chromosomes (a translocation) can cause a gene fusion. When a protein called menin interacts with MLL fusion proteins, an MLL leukemia results. Translocations in MLL are involved in 50-80 percent of infant leukemias.

Patients with the MLL leukemias have a very poor prognosis with current therapies, with only about one-third of patients surviving five years after diagnosis. Conventional chemotherapies are highly toxic and not very effective for patients with MLL leukemias. Dr. Grembecka's team has been working on small molecule drug compounds that inhibit the binding of menin to the MLL fusion proteins without affecting normal cells. Such protein-protein interactions are generally considered "undruggable" and very difficult to target.

Initially, Dr. Grembecka was able to create compounds that disrupted the interaction in the lab but couldn't evaluate them in living organisms because the molecules had poor pharmaceutical properties. Through TAP, LLS engaged chemists to improve the properties that produced lead compounds that tested successfully in animal models. Later, LLS introduced Kura Oncology to provide funding and expertise to help advance this project into the drug development pipeline.

This investment by Kura Oncology is further evidence of LLS's successful track record with venture philanthropy to help bring promising therapies to patients more quickly.

Understanding the Biologic HOW

Driving a car or surfing the Internet doesn't usually require a thorough understanding of the inner workings of the vehicle or device. When it functions, we are satisfied. But for a scientist, knowing the mechanisms of action can lead to a new therapeutic target. Which is why LLS funds research across the continuum:

- learning HOW something works (Basic Research)
- translating lab knowledge into potential therapies (Translational Research)
- testing safety and effectiveness and comparing to current therapies (Clinical Trials)
- expediting the drug discovery and development process (Therapy Acceleration Program)

In the important category of basic research, LLS recently approved a five-year grant to Christopher R. Vakoc, MD, PhD, at Cold Spring Harbor Laboratory. He is investigating the molecular mechanisms of a possible Achilles' heel in acute myeloid leukemia (AML). In this project, he is studying a class of epigenetic regulatory proteins that contain a novel structural domain known as bromodomains (BRDs). The BRD4 protein in this group can increase the expression of genes that promote cancer cell growth and survival.

Although Dr. Vakoc identified the BRD4 protein five years ago, it was considered "undruggable." About that time, James Bradner, MD, at Dana-Farber Cancer Institute, published a paper about a molecule developed in his lab that he named JQ1. It suppresses BRD4 activity and in doing so inhibits the expression of a master control gene called MYC. When this gene is turned off, cells are convinced they are normal rather than cancer cells.

Thanks to Dr. Bradner's open-source availability of JQ1 information, Dr. Vakoc was able to test the molecule in mice and discovered it had a robust effect in AML. It can make cancer cells shed their leukemia characteristics and mature into normal white blood cells. Today, multiple Phase 1 clinical trials are testing BRD4 inhibitors in humans including LLS-supported trials in our Therapy Acceleration Program partnership with Constellation Pharmaceuticals.

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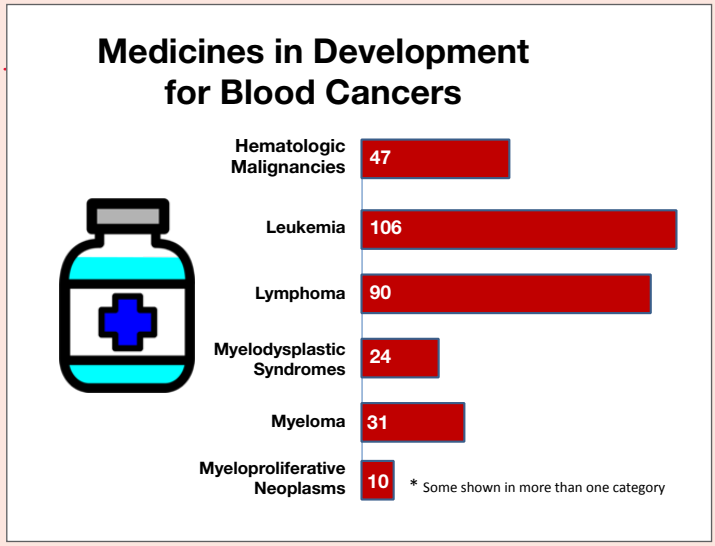
Through his studies to understand the molecular and genetic underpinnings of cancer, Dr. Vakoc looks to identify more weak spots to serve as next-generation epigenetic drug targets in B cell malignancies. With his new LLS funding, he is studying the TRIM33 protein that acts as a cancer promoting gene (oncogene) by preventing apoptosis, the natural biological process that tells unwanted cells to die. Although BRD4 and TRIM33 activities are similar, TRIM33 is much more specific.

Treatment Pipeline is Robust

LLS and the Pharmaceutical Research and Manufacturers of America (PhRMA) reported recently that more than 240 medicines are in development for people with leukemia, lymphoma, myeloma and other forms of blood cancers.

This is an extraordinary time of great promise in which a wide variety of approaches offer opportunities for more precise treatments and fewer side effects. Such a robust pipeline is the collective product of laboratory researchers, clinician-scientists, trial participants, commercial enterprises and–importantly–the forward-looking donors who fuel that progress. Thank you.



Advocacy Volunteers Improve Access

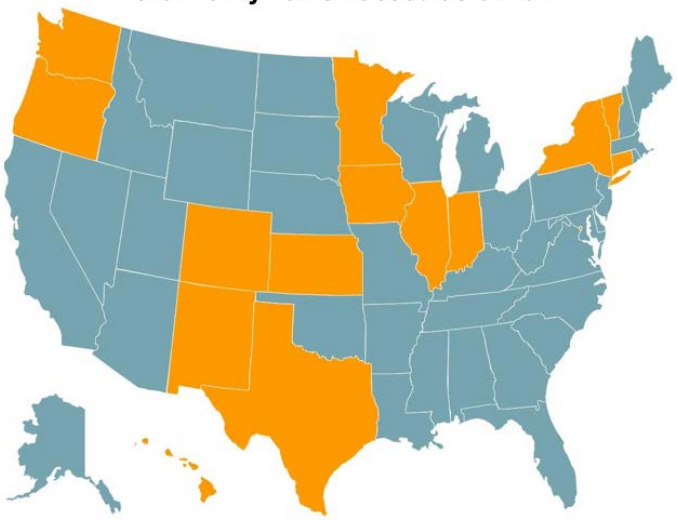
In recent years, drug therapies that are orally administered have become more prevalent in cancer treatment. Today, more than 25 percent of drugs in the pipeline are oral medications. But because health insurance plans have not kept pace with this trend, patients who are prescribed an oral therapy may find themselves facing out-of-pocket costs of thousands of dollars for a one month's supply of a medication.

This is because IV/injected cancer treatments have traditionally been covered under a health plan's medical benefit, where the out-of-pocket cost is typically a moderate, flat co-payment. However, oral therapies are usually covered under a pharmacy benefit, where patients often pay a percentage of the drug's cost, sometimes as much as 40 or 50 percent. Such expensive cost-sharing is known to cause some patients to alter the prescribed treatment regimen or abandon it altogether. This can lead to additional treatments, costly hospitalizations and less-than-optimal outcomes.

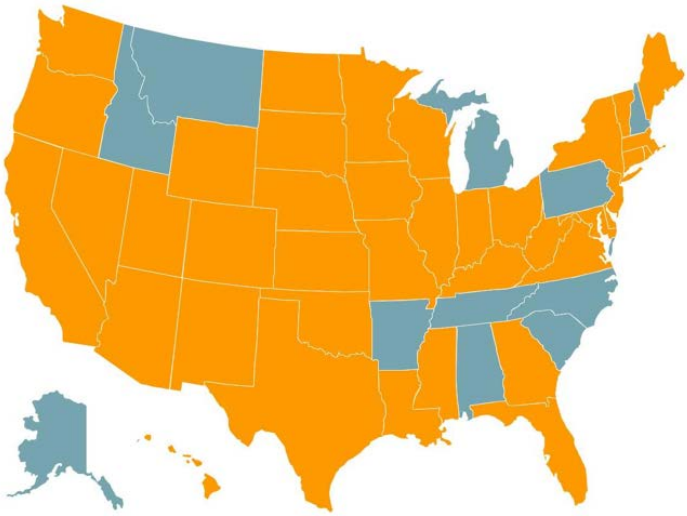
Thanks to the steadfast efforts of advocacy volunteers from LLS and partner organizations, thirty-nine states and the District of Columbia now have parity laws in place. These laws prohibit health plans from requiring patients to pay a higher out-of-pocket cost for an oral therapy than for a therapy that's administered by IV or another method. In states with parity laws in place, patients can reliably expect fair and consistent coverage for cancer therapies, regardless of how those medications are administered.

LLS's advocacy team regularly works with patients, family members, and healthcare providers to give the blood cancer community a voice in state and federal policy and legislative arenas. To become an advocate for LLS, contact Jon Hoffman at jon.hoffman@lls.org.

Oral Parity Laws Passed as of 2011



Oral Parity Laws Passed as of 2015



Your Gift Saves Lives

Please remember The Leukemia & Lymphoma Society in your will or as a beneficiary in your retirement plan. For information please contact:

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561-312-3573 or **legacy@LLS.org**