

# HIGHLIGHTS

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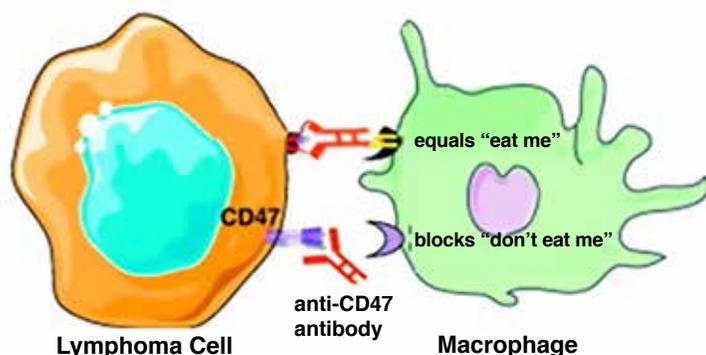


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Progress happens when smart money and smart research meet. The Leukemia & Lymphoma Society (LLS) values the generosity of donors who make life-saving advances possible.

## TAP Tests Two Immunotherapies for Lymphoma Patients

**D**ifferent approaches to activate the immune system are demonstrating remarkable anticancer activity in patients. One method uses immune checkpoint blockers to release the brakes on immune system T cells. Using this approach, Stanford University researchers funded by LLS, Irv Weissman, MD, and Ravi Majeti, MD, PhD, studied macrophages. This is a type of immune cell that patrols the body and chews up damaged cells. If a macrophage latches onto a normal cell, a protein known as CD47 sends a “don’t eat me” signal. But lymphoma and leukemia cells are clever and use CD47 to trick the macrophages into ignoring them and letting them grow as cancer.

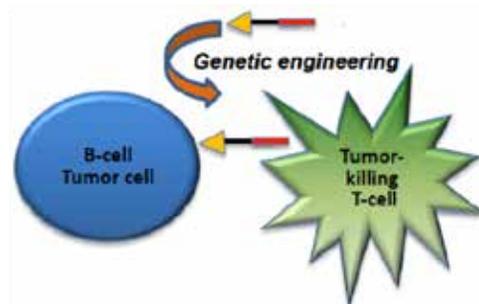


In pre-clinical mice models, Drs. Weissman and Majeti used an antibody to block the “don’t eat me” signal and stimulate the immune system to recognize the cancer cells as invaders. When they added rituximab as an “eat me” signal, the therapy delivered a one-two punch.

Today, the LLS Therapy Acceleration Program (TAP) is leveraging this academic grant with a \$4 million

investment to Forty Seven Inc., the company founded by Drs. Weissman and Majeti. Forty Seven’s multi-site, Phase 1b/2 clinical trial is combining its antibody known as Hu5F9-G4 with rituximab in patients with diffuse large B-cell lymphoma and follicular lymphoma. The trial is currently enrolling participants at sites in California, Illinois, Missouri and Tennessee.

In a different immunotherapy approach known as CAR-T, immune T cells are extracted from a patient and altered in the lab to



contain an artificial gene that produces a Chimeric Antigen Receptor. The CAR targets CD19, a protein on B-cell lymphomas and leukemias. When re-infused back to the patient, the engineered cells act as a “living drug” that can multiply into thousands of new cancer-fighting T cells.

Two years ago, TAP partnered with Kite Pharma to help develop the CAR-T therapy known as KTE-C19. In February 2017, Kite released impressive clinical trial results from a multi-site phase 1 and 2 trial in patients who are refractory (resistant to treatment) with diffuse large B-cell lymphoma and two rare lymphomas – primary mediastinal B-cell lymphoma and transformed follicular lymphoma. More than a third (36 percent) showed no sign of disease six months after a single treatment. This was about the same

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# Liquid Biopsy Offers Diagnostic Breakthrough

New targeted therapies and transplantation strategies are producing good outcomes for patients with currently incurable diseases such as mantle cell lymphoma. But achieving cures will require accurate monitoring of minimal residual disease after treatment. An LLS grant recipient in Australia, Sarah-Jane Dawson, PhD, at the Peter MacCallum Cancer Centre in Melbourne, is studying “liquid biopsy” to allow patient-specific cancer mutations to be tracked in real time.

**Liquid biopsy enables real-time tracking of therapy response so that rapid adjustments can be made if the patient relapses or is not responding to treatment.**

In the study of liquid biopsies, a test on a sample of blood looks for cancer cells from a tumor (known as circulating tumor cells or CTCs) or from tiny fragments of DNA shed by tumor cells into the bloodstream (known as circulating tumor DNA or ctDNA). The major difference between the two is that ctDNA is

much more abundant in the bloodstream. A typical blood sample would yield a handful of CTCs but possibly hundreds of ctDNA, making it easier to detect.

There are significant variations among tumor cells so that a single tissue biopsy will not precisely reflect a tumor’s composition. But dying cancer cells shed DNA into the bloodstream so ctDNA accurately mirrors the disease across the body. Gene sequencing machines can quickly decode millions of the circulating DNA fragments. Results can be compared with the human genome map to spot patterns of rearranged DNA that are telltale signs of a tumor. This enables real-time tracking of therapy response so that rapid adjustments can be made if the patient relapses or is not responding to treatment.

Liquid biopsy is not yet a substitute for a bone marrow or lymph node biopsy at diagnosis but it does reduce the number of biopsies a patient must endure throughout treatment and has potential to significantly reduce costs.

Dr. Dawson is validating the utility of ctDNA in a combination study of ibrutinib and venetoclax for patients who have relapsed or are resistant to therapy for mantle cell lymphoma.

## A New Approach for the Elusive CML Cure

In an effort to finally cure chronic myeloid leukemia (CML), Craig Crews, PhD, at Yale University, is collaborating with Brian Druker, MD, at Oregon Health & Science University, to completely eradicate all leukemia cells bearing the “Philadelphia chromosome.” CML occurs when pieces from two chromosomes break off and attach to each other to produce the Philadelphia chromosome. The abnormal fusion, known as BCR-Abl, produces a cancer-causing protein that causes uncontrolled growth of defective white blood cells.

Current therapies, including imatinib (Gleevec) and dasatinib (Sprycel) inhibit the function of the abnormal protein so that CML cells die out, resulting in a chronic but manageable disease. But in about 30 percent of patients, persistent leukemic stem cells survive, preventing a complete cure and requiring continuous lifetime treatment. Over time, some patients become resistant to treatments.

Some scientists believe that stem cells use BCR-Abl as a protein scaffold to seek compensating pathways. They hypothesize that knocking out the scaffold could produce a CML cure. Dr. Crews is using a new approach that uses PROteolysis TArgeting Chimeric molecules (PROTACs) that degrade unneeded or damaged protein to eliminate the scaffold rather than the current therapy that inhibits BCR-Abl.

The PROTAC technology uses ubiquitins, small tags that regulate processes in the body. Ubiquitin, referred to as the molecular “kiss of death,” is known for its role in apoptosis, the process by which cells are programmed to die. Because the small molecules require only transient binding to any surface of the target protein, the approach can be useful for so called “undruggable” proteins. If targeted degradation of BCR-Abl is successful, it could be an effective strategy for either initial treatment or secondary treatment following the onset of resistance.

## New AML Therapy **Approved**



**M**utations in specific genes are found in many cases of acute myeloid leukemia (AML). One of them – the FLT3 mutation – is detected in about one third of patients and is associated with poor outcomes and shorter survival.

On April 28th, the FDA approved Midostaurin (Rydap<sup>®</sup>) as a new therapy for newly diagnosed AML patients with the FLT3 mutation.

With the exception of a drug that was approved in 2000 and later withdrawn because of its toxicity, this is the first significant advance for AML patients in 40 years. Midostaurin is used in combination with chemotherapy and has been supported by LLS since 2001 in pre-clinical and early clinical trials.

### **The FDA-approved Midostaurin therapy ... is the first significant advance for AML patients in 40 years.**

According to Richard Stone, MD at Dana-Farber Cancer Institute, this is the first step in applying the theories of personalized medicine to patients with AML.

Another investigational therapy is on track to yield a second approval for AML patients this year. Vyxeos<sup>™</sup>, the innovative reformulation of standard chemotherapies encased in liposomes to optimize the ratio and delivery of the drugs, was developed by Celator Pharmaceuticals before it was acquired in 2016 by Jazz Pharmaceuticals. The LLS Therapy Acceleration Program supported the Phase 2 and Phase 3 trials.

## **TAP tests Two Immunotherapies for Lymphoma Patients** *continued from cover*

as the three-month reading, suggesting lasting benefits for those who respond well. Of the 101 patients in the study, 82 percent had their cancer shrink at least by half.

Safety results were solid with only 13 percent developing cytokine release syndrome, a dangerous condition in which the immune system overreacts. The rate was lower than in some other CAR-T therapies and it fell during the study as clinicians detected and treated the condition sooner.

Kite Pharma recently applied for FDA approval that could lead to launch and commercialization of KTE-C19 by year end.

## Pediatric Specialist Studies Rare Form of Leukemia

Cancer is the leading cause of death of children in the United States and pediatric blood cancers represent about half of those cancers. Yet financial support for pediatric cancers is limited. The National Cancer Institute cut funding for pediatric cancer research by an inflation-adjusted 24 percent during the decade ending 2015. Pharmaceutical company interest remains low because the market is small and unprofitable. Remarkably, in the past 20 years, the FDA has approved only three new drugs exclusively for pediatric patients.

LLS funds blood cancer research based on unmet need rather than profit potential. A grant to Charles G. Mullighan, MD, a pediatric specialist at St. Jude Children's Research Hospital, supports the study of acute erythroid leukemia (AEL), a rare and aggressive subtype of acute myeloid leukemia (AML). Patients with AEL are treated similarly to patients with other types of AML, with chemotherapy-based regimens, but it is commonly resistant to chemotherapy. The prognosis is poor with a median survival of just 17 months.

Because of the limited understanding of this rare condition, Dr. Mullighan used genomic profiling to identify the genetic mutations driving the leukemia. He identified certain mutations found exclusively in childhood AEL. With the genomic data, he established engineered mouse models in which he will test new targeted therapies. Dr. Mullighan's work is highly innovative and addresses the need for precision medicine approaches in rare leukemias that lack effective therapies.

# Patients and Patience: Keys to Clinical Trial Success

One in ten clinical trials are discontinued, not because of poor results, but because of an insufficient number of enrolled patients. In orphan diseases like blood cancers, it can be especially challenging to find participants who meet the specified criteria.

For patients, the chief obstacles to participation are a lack of awareness and the complexity of identifying a clinical trial that is appropriate. LLS has been providing information and resources to patients for 20 years through the Information Resource Center and of 2,000 inquiries monthly, about a quarter of them seek help with clinical trials.

Three years ago, LLS launched a pilot program to improve the patient experience to identify and connect with appropriate trials. The patient-centric goals of the Clinical Trial Support Center (CTSC) are to explain options, evaluate whether a trial is appropriate and to serve as a hub of internal and external resources to provide guidance from enrollment through the course of the trial. In a typical call center, database-trained operators enter search terms such as age, diagnosis and geography to build a list of options for the patient to discuss with their physician. The list often includes trials for which the patient is not eligible, for any number of reasons the searcher was not qualified to evaluate. When presented with the list, the healthcare provider needs

time to engage in a detailed discussion with the patient.

In our CTSC, two highly-qualified nurses who understand blood cancers, the standard of care, and emerging therapies complement healthcare providers' efforts to serve patients. They educate the patient about trial risks and benefits before a thorough assessment of the diagnosis, health status, prior treatments, financial and insurance circumstances, travel and lodging needs, and their support network. With strong connections to trial sites and sponsors, they can determine eligibility, such as mutation requirements, and whether a trial is still open for enrollment.

The majority of referrals to the CTSC last year resulted in trial enrollments. On average, there were 15 interactions among the patient, family, healthcare provider, trial site and pharmaceutical company sponsor. Of those who did not enroll, reasons include restrictive trial criteria, a rapid deterioration in health status, an inability to travel, or insurance issues.

Evaluations of the program so far indicate that the key determinant of success is TIME. When trained professionals have the time to educate, evaluate, search, connect and support, a patient is more likely to consider a clinical trial as a life-saving option for their treatment.



## I support LLS because...



... the organization shows too much promise for me to stop. Back in 2003, I encountered a purple-shirted group of cyclists while training for my first triathlon. They were fundraising for LLS through Team in Training. After so much self-focus—had I run enough? Was I swimming well?—I vowed to do my next race with TNT. In 2004 I raced St. Anthony's Triathlon in honor of a boy (diagnosed at age 7, now 24) whose parents owe his survival in large part to LLS research. At the race, I met one person after another who had been touched by blood cancers. Their strength and will to support the cause inspired me to stay with TNT for another ten years.

I stopped racing, but my husband and I continue to support LLS—we've seen the power of research, and recently experienced it first hand when my brother-in-law was diagnosed with AML. One year and one stem cell transplant later, he is doing far better than we might have hoped. We are determined to help LLS advance innovative research, so his health will continue to improve, so more patients will enjoy similar success, so that one day, hope will be replaced by the certainty of a cure.- Lisa Kristel (pictured with husband, Steven), Long Island, NY

**To support research in the area of greatest concern to you, contact us at 1-888-773-9958.**