Activation of the immune system is not a new approach to treating cancer; LLS has been funding such research for two decades. But more recent knowledge of immune system mechanisms and the technical achievements to engineer T-cells and mass produce sophisticated antibodies to recognize cancer cells have accelerated to a new level.

Three approaches to activate the immune system are demonstrating remarkable anticancer activity in patients. They are immune checkpoint antibodies, chimeric antigen receptor T-cell therapy (known as CAR-T) and bi-specific antibodies.

Immune checkpoints are molecules that either stimulate or inhibit immune system T-cells. Together, the stimulatory and inhibitor molecules moderate the duration and strength of an immune response to protect tissues from damage when responding to an infection. Some cancers use inhibitory molecules, including those known as PD-1 or CTLA-4, as an immune system brake to evade attack. In recent years, scientists have had some success in using checkpoint antibodies to block the inhibitory molecules, release the brake and allow the immune system to function normally to fight cancer.

In the chimeric antigen receptor approach, immune T-cells are extracted from a patient and engineered to sharpen their ability to spot cancer. When re-infused back to the patient, the T-cells target cancer cells, proliferate and kill the tumor. Importantly, the engineered cells can be made to recognize unique antigens on different tumor types.

The third type of therapy combines two antibodies. The unique quality of this therapy is its two binding sites—one that binds to the tumor marker and one that activates the immune system.

LLS funds investigators in all these approaches. In the Stanford University lab of Ronald Levy, MD, scientists are using checkpoint blockers in a variety of ways. Holbrook Kohrt, MD, blocked CTLA-4 by injecting a checkpoint inhibitor (ipilumumab) directly into the tumor. This innovative method induced a systemic, whole body response. When combined with low-dose, local radiation, this removes the checkpoint brake using 1/10th of the usual dose, thus greatly reducing toxicity.

Dr. Levy is also combining ipilumumab with a ready-made vaccine, CpG, to stimulate the immune system. In a Phase 1-2 clinical trial, low grade B-cell lymphoma patients are treated by direct injection followed by local radiation. The trial is currently enrolling patients.
In early 2016, Bernie and Ethel Garil’s vision will emerge as a tangible tool for people concerned about blood cancers. Their son Michael developed leukemia at an early age and died in 2006 after years of toxic treatments and severe side effects. Bernie did not believe that his son’s side effects were isolated events but found that no information registry was available to confirm his opinion. Now, after several years of persistence, guidance and generosity, a significant new resource is ready to launch.

In partnership with Boston-based Unitio, the LLS Community will unite blood cancer patients, caregivers, and healthcare professionals. By leveraging the power and reach of digital technology, the new tool will create a social network among people touched by blood cancers. Users can engage with each other and with LLS to find support and resources across all types of blood cancers.

Many features currently found on the LLS website and in discussion boards will be found in the new online community. For example, users can find news about treatments and engage with others in discussions about their area of concern. There are two dozen discussion groups segmented by disease types and by topics such as Survivorship, Transplant, Fertility & Pregnancy, Just for Teens, and Parents of Young Adults.

Importantly, the large and diverse group will be empowered to participate in the research process by providing the scientific community with actionable patient data and insights about experiences and unmet needs. Surveys for patient users and regular polling will identify patterns of treatment so that outcomes can be analyzed and trends can emerge.

As the community builds, this will become a powerful tool for reaching newly diagnosed patients, educating patients and caregivers throughout their cancer journey, and networking among each other to share information about treatments and side effects. As a platform for surveys and research, the data collection will help to hasten the pace of therapeutic advances.

Join the community now at community.lls.org.

Dr. Stephen Ansell at the Mayo Clinic found that T-cells can become exhausted by chronic immune stimulation. The exhausted cells, which express PD-1, are associated with a poor prognosis and a likely transformation to an aggressive disease. He is investigating an antibody that could block PD-1 and reactivate the immune system in patients with follicular lymphoma.

In CAR-T investigations funded by LLS at University of Pennsylvania and at Memorial Sloan Kettering Cancer Center, the treatments eliminated all trace of leukemia and lymphoma in as many as 90 percent of patients who had run out of other options. And in LLS’s partnership with Kite Pharma through the Therapy Acceleration Program (TAP), engineered T-cells target CD19, a protein expressed in many B-cell lymphomas and leukemias. The multi-center trial is advancing CAR-T, evaluating safety and efficacy of treating patients with refractory diffuse large B-cell lymphoma as well as two rare lymphomas—primary mediastinal B-cell lymphoma and transformed follicular lymphoma. In late 2015, the FDA granted breakthrough therapy status on this investigational treatment.

A bi-specific antibody is being tested in partnership with a German company, Affimed. This Phase 2 trial is investigating a safer therapy to enhance the quality of survivorship for Hodgkin lymphoma patients. Current treatments involve cytotoxic drugs and radiation that are likely responsible for secondary tumors and other long-term side effects. Combining the antibody with checkpoint blockers could further augment its effectiveness.

More knowledge is needed to maximize the potential of immunotherapies, including identifying biomarkers to select patients most likely to respond and antigens to be used as vaccines, understanding mechanisms of toxicities and how existing agents might be repurposed to engage the immune system. In pursuit of answers, LLS and the Switzerland-based Rising Tide Foundation for Clinical Cancer Research are inviting global applications for US $1.8 million in collaborative grants. The focus is immunotherapy research with the highest potential for patient impact.
Too often, promising ideas in the lab languish in the “Valley of Death,” the space between laboratory discovery and the commercial development of new therapies. Were it not for years of sustained investment by LLS in the 1990s, Gleevec® would have been among those casualties. To advance prospective therapeutics, the LLS Therapy Acceleration Program (TAP) invests in pre-clinical and early phase trials to reduce risk and make commercial development more attractive. Dozens of prospective therapies have moved to clinical use already and 19 current investigations, including two described in the immunotherapy article in this newsletter, are accelerating more possibilities.

With an earlier LLS grant, Arthur Frankel, MD, designed and produced a novel agent consisting of a portion of diphtheria toxin fused to blood cell growth factor, IL-3. This investigational therapy binds selectively to leukemia stem cells and helped patients with advanced acute myeloid leukemia (AML). Receptors for IL-3 are abundant on cancer stem cells within AML and in other leukemias and lymphomas including blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare lymphoid malignancy for which there is no standard of treatment.

Recognizing the potential of Dr. Frankel’s investigational therapy in BPDCN patients, LLS partnered with the biotechnology company Stemline to advance its targeted therapy, SL-401. Recently released data indicate that SL-401 demonstrated pre-clinical activity against a variety of indications including AML, CML, lymphomas and myeloma. In an LLS-supported Phase 2 trial for BPDCN patients, multiple consecutive cycles of SL-401 produced an 86 percent overall response rate. That was a 100 percent overall response as a first-line therapy and 60 percent in relapsed and refractory patients. The trial continues to enroll patients.

Donor stem cell transplantation can be the best curative option for AML patients but about half of transplant patients relapse because of residual stem cells. Researchers at University of Colorado showed that a molecule known as Hedgehog and its molecular collaborators are hyperactive in leukemia stem cells. A drug called PF-04449913 has been found to inhibit Hedgehog activity and was well tolerated in an early trial for acute leukemia patients. LLS’s TAP is supporting a Phase 2 clinical trial using PF-04449913 as a monotherapy for 20-30 AML and MDS patients who are at high risk for post-transplant relapse. The success of this proof of concept trial has caught the attention of a large pharmaceutical company that looks to expand the enrollment.
Optimism continues to grow for those seeking less toxic therapies for chronic lymphocytic leukemia (CLL). The *New England Journal of Medicine* recently published data about ibrutinib, the therapy for previously treated CLL patients. Ibrutinib targets the BTK protein found on the surface of B-cells that plays a central role in sending growth signals to cells. When inhibited, the CLL cancer cells die. The data by two LLS-funded researchers, Thomas Kipps, MD, PhD, at University of California at San Diego and his collaborator, Jan A. Burger, MD, PhD, of MD Anderson Cancer Center, compared ibrutinib to a standard chemotherapy, chlorambucil. They found ibrutinib to be far superior. The Phase 3 study was in older adults (median age 73) who had not been previously treated. They found that the risks of progression and death were both 84 percent lower with ibrutinib than with chlorambucil. With this data, ibrutinib might replace chemotherapy as a first-line treatment for newly diagnosed CLL patients.

When ibrutinib was first approved in 2014, it was the result of a Phase 3 clinical trial led by LLS-funded researcher John Byrd, MD of the Ohio State University. Now, Dr. Byrd has data on another investigational therapy for CLL—acalabrutinib (ACP-196). This potent second-generation BTK inhibitor appears to be even more effective and targeted than ibrutinib and with less toxic side effects. The Phase 1 and 2 data for ACP-196 show that 95 percent of relapsed CLL patients in the trial achieved partial responses or stable disease.

This potent second-generation BTK inhibitor appears to be even more effective and targeted with less toxic side effects.

And a team of Australian researchers led by Jerry Adams, PhD, and Andrew Roberts, PhD, are finding encouraging data in a Phase 2 trial of ABT-199, now known as Venetoclax, which received FDA breakthrough designation in 2015. It works not by directly killing cancer cells, but by controlling the programmed death of cells, a process known as apoptosis. In CLL, malignant cells fail to die because of an abundance of the BCL-2 protein that keeps them alive. As a result, healthy white blood cells, red cells and platelets are crowded out. Venetoclax interferes with the BCL-2 protein so that the cancer cells can die as programmed. Because it is administered orally, it is important that patients and clinicians are aware of its strong effects.

In trials, Venetoclax met its primary endpoint of achieving overall response rates in patients with relapsed/refractory or previously untreated CLL with chromosomal 17p deletion. About 30 percent of CLL patients who do not respond to therapy or relapse are found to be missing part of chromosome 17. Data from this trial will enable the drug to be submitted to the FDA for approval.

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“...of its commitment to patients. Their support has been vital for countless patients under our care and I value how LLS helps them in their physical and financial struggles.

Further, LLS support for my translational research has been critical for patients with cutaneous T-cell lymphoma. Long-term remissions for these patients are elusive and those with advanced stages have a poor prognosis. LLS funding made it possible to test a potent topical immune system activator that has shown very high response rates in patients for whom earlier therapies failed. This immune system stimulator may completely change our future treatment approach.

Ongoing LLS research grants have been instrumental in our ability to develop and define mechanisms of action of multiple novel drugs, several of which are now standard of care in our clinic.”

— Alain H. Rook M.D., Director, Cutaneous Lymphoma Program, University of Pennsylvania

To help advance research in the area of greatest concern to you, contact Richard Schneyer, vice president of Development at 1-888-773-9958 or richard.schneyer@LLS.org.

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The Leukemia & Lymphoma Society | 1311 Mamaroneck Ave, Suite 310 | White Plains, NY 10605