

Leukemia and Lymphoma

Research Update 2013

National Leadership

The Cancer and Blood Diseases Institute at Cincinnati Children's is developing leukemia and lymphoma treatments to cure kids and save lives in ways that were not possible just a few years ago.

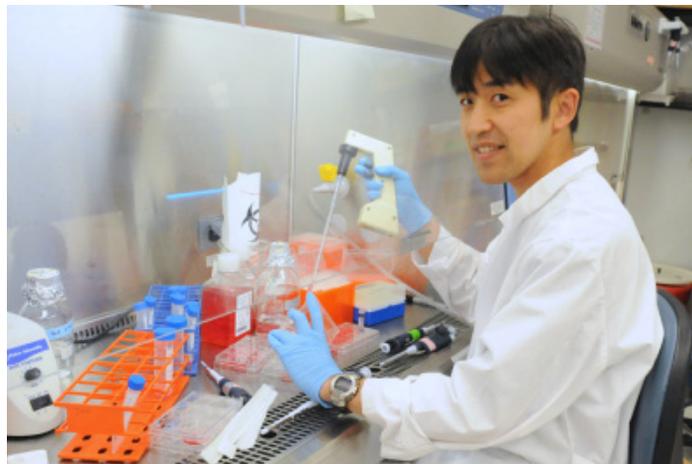
Leukemias are the most common childhood cancer and a major focus of basic science and drug-development research at Cincinnati Children's. While current treatments cure a majority of children and adolescents with leukemia, the treatment is harsh and we do not have good therapies for some high-risk or relapsed diseases. Cincinnati Children's researchers are leading the way to a cure for all leukemia patients.

Our laboratory researchers are probing the causes of leukemia and working as a team with our doctors to develop the next generation of innovative therapies, including improved bone marrow transplantation regimens and new targeted drugs that kill cancer cells without the serious side effects of traditional chemotherapy. Using sophisticated technology, our researchers are finding the "Achilles' heel" of leukemia cells to identify potential targets for new drugs.

Testing New Treatments for Leukemia

Cincinnati Children's researchers are currently testing several new drugs for high-risk and relapsed leukemia:

- Michael Absalon, MD, PhD is testing CPX-351 in patients with relapsed or refractory hematologic malignancies including AML, ALL and aggressive lymphomas.
- Christine Phillips, MD: is testing AR-42 in combination with decitabine in relapsed AML.
- Maureen O'Brien, MD is testing: sirolimus plus multiagent chemotherapy for relapsed acute lymphoblastic leukemia/lymphoma; SGN-CD19A for relapsed pre-B acute lymphoblastic leukemia/lymphoma or Burkitt's leukemia/lymphoma; CD19-CD3 antibody blinatumomab in children with relapsed pre-B acute lymphoblastic leukemia.



Susumu Goyama, PhD, investigates better disease models

Creating Models of Leukemia for New Treatments

Cincinnati Children's researchers James Mulloy, PhD, and Yi Zheng, PhD, are leading the fight against very aggressive forms of childhood leukemia. Leukemias with mutations in a gene called MLL tend to be resistant to contemporary chemotherapy approaches and very difficult to treat.

Drs. Mulloy and Zheng have developed a new model in mice for AML using human blood stem cells altered to carry the MLL gene. The Mulloy lab was among the first in the country to successfully transform a human blood stem cell into a leukemia cell in this way. This mouse model can be used to safely test potential new drugs.

Research Highlights

Many researchers at Cincinnati Children's examine how normal blood cells are transformed into leukemia cells and why the body's defenses against DNA damage and cancer don't always work.

Mohammad Azam, PhD, continues his research on the structure and function analysis of tyrosine kinases involved in the pathogenesis of leukemia. His lab is also investigating the molecular basis of "oncogene addiction" and potential ways to use this addiction to



The Cancer and Blood Institute's Drug Discovery Center features this next-generation DNA genomic sequencing machine

develop leukemia therapies. He also models human leukemia in mice using ES and patient derived cells. Jose Cancelas, MD, PhD, studies how the body produces new blood cells inside the bone marrow and how mutations in a gene called BCR-ABL cause a type of ALL that resists most current treatments. Dr. Cancelas's laboratory has identified possible targets for drugs in among the proteins created by BCR-ABL.

H. Leighton Grimes, PhD, investigates T cell acute lymphoblastic leukemia which is treated with high dose chemotherapy with serious long lasting side effects. The Grimes lab found that these leukemias are highly dependent on the expression of a single transcription factor. Inhibiting this factor's expression cured the leukemias in animal models in the lap without therapy-limiting side effects.

Gang Huang, PhD, focuses on the genetic changes that turn normal blood cells into leukemia. He has demonstrated that the genes AML1/CBF-beta and MLL work together to suppress cancer cells but that mutations to these genes cause the majority of AML, ALL, and myelodysplastic syndromes.

Ashish Kumar, MD, PhD, studies a gene called MEIS1 that is over-active in leukemia. Work from Dr. Kumar's lab shows that blocking MEIS1 could be an effective way to fight cancers which are resistant to current therapies.

Qishen Pang, PhD, studies the role of the cell-signaling protein TNF-alpha in bone marrow failure, a condition that can lead to leukemia. His work has led to a Cincinnati Children's study of etanercept, a drug that blocks TNF-alpha, in children with early bone marrow dysfunction to prevent bone marrow failure and leukemia.

John Perentesis, MD, studies the causes of leukemia in children with Down syndrome, who have a significantly higher risk of developing the disease, as well as ways to improve treatment. His laboratory has shown that genetic differences in how individuals neutralize oxidants contribute significantly to the risk of leukemia. As chair of the national Children's Oncology Group Myeloid Relapse Committee, Dr. Perentesis has developed a series of clinical studies to test new therapies for AML.

Daniel Starczynowski, PhD, studies myelodysplastic syndromes (MDS), conditions that result in defective white blood cell production and an increased risk of leukemia. Dr. Starczynowski's lab is identifying previously unknown genetic mutations related to MDS, focusing on the NFkB signaling pathway, which may lead to the development of new drugs.

Yi Zheng, PhD, Director, Division of Experimental Hematology and Cancer Biology, leads a search for small molecule inhibitors that can disrupt the function of cancer stem cells. His lab has already discovered several such lead small molecules. The molecule "CASIN" can push leukemia-initiating cells into the bloodstream, where they become much more vulnerable to chemotherapy and may make stem cell transplants much more effective. Recently, the Zheng lab discovered "Rhosin" and another inhibitor Y16, molecules that can disrupt a key cell signaling cascade involved in cancer cell proliferation and invasion. These novel small molecule inhibitors are being applied to acute myeloid leukemia and acute lymphoid leukemia in animal models.

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