



CREATING BETTER TREATMENTS FOR ALL

Breakthrough exploits vulnerabilities of radiation-resistant leukemia cells

Acute lymphoblastic leukemia (ALL) is a cancer of malignant white blood cells that multiply with damaging and deadly abandon. It's the most common form of pediatric cancer, and just 40 years ago, only one in five children survived.

The development of powerful chemotherapies has changed that: almost 80 percent of patients these days can expect to be cured.

But in the other 20 to 25 percent of patients with ALL, the cancer returns, requiring additional rounds of intense chemotherapy and radiation. Doctors must sometimes resort to the extreme measure of total body irradiation and very high-dose “supralethal” chemotherapy to kill as many leukemia cells as possible—relying on bone marrow transplantation to restore healthy cells also killed in the process.

Unfortunately, in the case of early relapse, even these drastic measures usually fail. Less than 20 percent of ALL-relapse patients remain disease-free over the long term. Most die within one year of relapse because, as it turns out, these leukemia cells are intrinsically resistant to radiation.

“Unlike bacteria and antibiotics, where the germs become resistant after repeated exposure, with radiation resistance, some leukemia cells are resistant even if the patient had never been treated with radiation before,” says Fatih M. Uckun, MD, PhD, an ALL expert at The Saban Research Institute of Children’s Hospital Los Angeles and former Stohlman Memorial Scholar of the Leukemia Society of America.

To reduce and perhaps prevent ALL relapses, scientists needed to discover why leukemia cells seemingly defy radiation. “We knew that we could kill radiation-resistant leukemia cells if we only knew what made them so resistant, so we set out to determine the mechanism,” says Uckun, professor of Research Pediatrics at the Keck School of Medicine of the University of Southern California (USC) and a member of the Developmental Therapeutics Program in the Norris Comprehensive Cancer Center at USC. “Once we determined the mechanism, the next step was obvious: to rationally design a drug that would take out that specific target.”

In late 2010, a research team led by Uckun did just that, developing a novel approach that renders leukemia cells more vulnerable to radiation therapy. The scientists showed in a proof-of-principle study that their approach works in mice challenged with an otherwise invariably fatal dose of radiation-resistant human leukemia cells.

“The goal was to not only kill more leukemia cells, but more importantly to do so with low doses and so avoid short-term and long-term side effects associated with higher doses of radiation,” he says.

The team’s breakthrough came in two parts.

First, researchers discovered a link between an enzyme called SYK tyrosine kinase and radiation resistance in leukemia cells. In normal immune system cells, SYK kinase is one of several gatekeeper proteins conducting similar functions. Leukemia cells, however, have genetic defects in the regulatory apparatus that normally keep the survival-promoting function of SYK in check.

As a result, says Uckun, the SYK enzyme “is hijacked to a unique and non-redundant survival-promoting role. That’s how leukemia cells survive high doses of radiation.” The work was published in back-to-back papers in the *Proceedings of the National Academy of Sciences*.

The scientists concluded that if the SYK kinase pathway in leukemia cells could be blocked, cancer cells would be less resistant to radiation and more likely to be completely eradicated by total body irradiation (in the context of bone marrow transplantation). Thus, the chances of relapse would be significantly reduced.

The second part of the breakthrough was the discovery of a drug specifically designed to target the SYK kinase pathway. Dubbed C-61, the drug binds to and blocks SYK kinase activity, leaving leukemia cells fatally sensitive to radiation.

In experiments using mice carrying human leukemia cells, injections of C-61 prior to radiation and afterward were much more effective in killing cancer cells than current approaches. This work was published in *Radiation Research*, the journal of the Radiation Research Society.

Uckun and his colleagues have since developed a stronger, second-generation SYK inhibitor and hope that it might provide the foundation for personalized radiation therapy regimens that are less toxic and more effective.

While creating better treatments for ALL has been the scientists' primary focus, Uckun says recent studies suggest SYK kinase is a key player in other cancers, such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute myeloid leukemia and head and neck cancer.

"Further development of SYK inhibitors like C-61 may lead to therapeutic innovation in other forms of leukemia and non-Hodgkin's lymphoma," he says. "Targeting SYK to overcome radiation resistance by combining a SYK inhibitor with radiation therapy would be a potentially paradigm-shifting treatment strategy."

Uckun will continue to pursue the use of SYK inhibitors as a new class of radiation sensitizers with a new \$1.7 million grant award from the National Cancer Institute.

In addition, he and his colleagues have joined the National Cancer Institute Alliance on Nanotechnology Against Cancer and have created nanoparticles of C-61 that are much more potent than the original drug. This work will be presented later this year at the Gordon Conference on Nanotechnology.

With another \$2.5 million grant award he received from the National Institutes of Health, Uckun says he hopes to develop clinically usable, state-of-the-art nanomedicine within five years.

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