

Research Horizons

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Relentless for a Cure



Welcome to *Research Horizons*, a bulletin from The Leukemia & Lymphoma Society, providing news on studies and recent findings in blood cancer research.

HIGHLIGHTS from

Acute Leukemia Forum 2006: Advances and Controversies in the Biology and Therapy of Acute Myelogenous Leukemia

MARCH 31, 2006, SAN FRANCISCO

The City by the Bay may have been the perfect meeting place for experts bent on pushing away the scientific fog that surrounds acute myelogenous leukemia (AML). The meeting, now in its 10th year, serves as a kind of annual clearinghouse of ideas as experts present and debate advances against the disease.

This year, especially, much of the research focused on AML's earliest origins in the stem cell – progenitor marrow cells that grow and change to form blood cells. In rare cases, something in that process goes awry, triggering AML or other malignancies. And while drugs that target mature, malignant cells can bring about remission, the presence of untreated leukemic stem cells leaves the nagging fear that someday the disease might return.

Targeting Differences

Because they give rise to every type of cell in the body, stem cells are essential to life. So, the challenge for researchers has been to identify and attack abnormal, malignant stem cells while leaving healthy cells alone.



Craig Jordan, Ph.D.

"Scientifically it's a very hot area right now, mainly because we haven't had the tools before to target these cells and develop the

necessary drugs," explained researcher Craig Jordan, Ph.D., associate professor of medicine, University of Rochester School of Medicine and Dentistry, and director, James P. Wilmot Cancer Center Hematologic Malignancies Translational Research Program.

With new, high-tech assays and other technologies now in place, the race is on to find biomarkers that single out leukemic stem cells, Dr. Jordan said.

One promising avenue has been a pro-cell-survival mechanism called the NF Kappa B pathway. "We're excited about this particular pathway because it is very strongly activated in leukemic cells but not normal cells," Dr. Jordan said.



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Cancer cells spread and kill for two reasons: They proliferate at high rates and they fail to undergo programmed cell death ("apoptosis") as normal cells do. The NF Kappa B pathway is a "molecular switch" that helps leukemic stem cells delay apoptosis and stay alive, even when threatened by chemotherapy.

Inhibiting NF Kappa B "would ideally kill leukemia stem cells, but not the normal stem cell," explained Dr. Jordan.

Speaking to the assembled experts, he said one agent, parthenolide, has already shown great promise in selectively targeting and destroying AML stem cells. However, parthenolide in its pure form is too unstable for use as a pharmaceutical.

"Luckily, we now have a Translational grant from The Leukemia & Lymphoma Society to try and get it into a more pharmacologically useful form, a chemical called dimethylaminoparthenolide," Dr. Jordan said.

Tests in larger animals, aimed at assessing the drug's toxicity, are already underway, with results expected by mid-summer. "If all goes well, we'd then go to the FDA and say 'OK, we want to try this out in patients,'" he said.

Other stem cell-targeted agents, also aimed at inhibiting NF Kappa B, are in development elsewhere, and Dr. Jordan said the field is breaking wide open.

"Focusing on the stem cell is actually a very old notion, but the tools haven't been there to pursue it," he said. "That's why it's been so exciting to come here and hear clinicians talking about it more and more."

Creating a Hostile Environment

Anyone who's ever rented a poorly heated, bug-infested apartment knows that if the situation isn't remedied their only real option is to leave.

According to Harvard Medical School professor of medicine David Scadden, M.D., that's the theory behind new research targeted indirectly at leukemic stem cells via their "microenvironment" in the marrow.



David Scadden, M.D.

"Cancers just don't show up anywhere, they go to very specific areas, so it's likely they have a real dependence on particular environments," explained Dr. Scadden, co-director, Harvard Stem Cell Institute, and chief of

hematologic malignancies at Massachusetts General Hospital's Cancer Center, Boston.

At the San Francisco meeting, Dr. Scadden outlined the preferred home of leukemic stem cells, a discrete, nutrient-rich region within bone. "We're researching this 'niche' to see if there's something different about the relationship it has with leukemic stem cells vs. normal cells," he said. "That gives us the potential of modifying this microenvironment in a way that can inhibit the abnormal cell, but allow the normal stem cell to survive."

Existing, safe pharmaceuticals may do just that, Dr. Scadden said. In a mouse model of AML, his team found that parathyroid hormone – an agent already used to fight osteoporosis – "enhanced the ability of normal stem cells to survive but decreased the ability of leukemic stem cells to survive." This ongoing research is partly funded by a Society grant.

According to the Harvard expert, this marks the "first proof of concept" that altering the leukemic stem cell's environment undermines its survival. "Parathyroid hormone is just one of many drugs that are being developed in this way – these drugs are all used in other contexts, mostly focusing on bone and bone diseases." Another bonus: Most of these well-tested agents come with few, if any, side effects.

Dr. Scadden cautioned that the parathyroid hormone results come from preliminary animal studies, and the drug is not yet ready for use by leukemia patients. He also stressed that these types of agents would likely be used as adjunct therapy.

"It wouldn't take the place of therapies that poisoned the cancer stem cell directly," Dr. Scadden said. "But if you poisoned it sufficiently so that you can get the numbers down, and then you made the environment more hostile, maybe you could boost the effect and reduce any chance for relapse."

An AML Vaccine?

Stem cell research wasn't the only field creating a buzz at the San Francisco meeting. Jeffrey Mollrem, M.D., The University of Texas M.D. Anderson Cancer Center in Houston, presented promising data on using the body's immune system to spot and destroy cancer cells – in other words, an AML vaccine.

"There are maybe a half-dozen places worldwide working on this," said Dr. Mollrem, chief, Section of Transplantation Immunology, Department of Blood and Marrow Transplantation. He said that a poor understanding of target antigens, plus disappointing results when it came to treating solid tumors, had kept researchers from searching for a leukemia vaccine.

That's beginning to change, however. Dr. Mollrem received funding from the Society to work in this area and presented findings from a preliminary study involving 45 patients, over half of whom were diagnosed with AML and in second remission (the others had either chronic myelogenous leukemia or myelodysplastic syndromes). Patients were followed for up to five years.

The trial focused on a vaccine targeted against a specific cell-surface protein, PR1. "It's a small little peptide that appears on the surface of leukemic

B-cells in the wrong place at the wrong time," explained Dr. Mollrem.

Vaccines work by priming immune system actors – in this case, killer T-cells – to recognize cell antigens like PR1 as "the enemy" and then destroy them if and when they appear.



Jeffrey Mollrem, M.D.

"With this vaccine, we are essentially expanding this T-cell population," Dr. Mollrem said.

With the study nearing its close, the Texas researcher said that a minority of patients have experienced long-term, molecular-level remissions. "I think it really shows promise," he said.

Dr. Mollrem stressed that "we've got to do this in randomized, more targeted and multi-center trials to show that it is a reproducible phenomenon." To that end, a randomized Phase III trial involving 240 patients is slated for launch at more than 40 centers across the United States this summer. "If that's positive, we could know the results in about three years, and it's entirely possible that some sort of vaccine might be ready within five years," Dr. Mollrem said.

But he also stressed that the jury is out on how effective any vaccine might be. One thing we do know is that immunization will only be useful for patients with relatively healthy immune systems. "It's not for patients with high blast counts. They've got such a weakened immune system to begin with, there's nothing for the vaccine to work with," he explained.

Still, the dream of building a sustained immune response targeted to re-emerging disease is closer to reality now than it has been in the past. "A successful vaccine would offer a lifelong immunity," Dr. Mollrem said. "If the leukemia tried to come back, your own immune system would take care of it."

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Transplanting Better, Earlier

A stem cell transplant's potential toxicity means it is often used only as a last resort – for example, in drug-resistant patients experiencing second remissions.



Fredrick Appelbaum, M.D.

But new research out of University Hospital's Carl Gustav Carus, in Dresden, Germany is suggesting that – for specific patients – stem cells from unrelated, matched donors might help cure AML if given earlier in the disease.

"That study moved the approach up and asked, 'In first remission, who ought to be treated?'" explained transplant expert Fredrick Appelbaum, M.D., head, Division of Medical Oncology, University of Washington School of Medicine, Seattle.

Not everyone should or can undergo this arduous therapy, said Dr. Appelbaum, who is also director of clinical research at Seattle's Fred Hutchinson Cancer Research Center.

In the German study, the researchers had 234 patients undergo standard induction chemotherapy. They then checked their hematologic and cytogenetic responses 14 days into treatment.

Some patients appeared to be responding well to the drugs. "In that case, you wouldn't want to go to allogeneic transplant if they had a good chance of

being cured with conventional therapy," said Dr. Appelbaum.

But other patients did not fare so well. "Some had unfavorable cytogenetics. Others had normal cytogenetics, but when you looked at their bone marrow you saw blast counts greater than 5 percent, for example," the Seattle expert said.

These were the "high risk" patients who were referred to matched, unrelated donor stem cell transplants.

The result: "Our own research, as well as the results of this German study, suggest that patients who are treated to first remission but who are at high risk of not responding to chemotherapy do respond well to allogeneic transplant – we can cure 50 to 60 percent of these patients," Dr. Appelbaum said.

He believes evidence is building that testing 14-day treatment responses during first remission, with an eye to transplant, might be a useful strategy. Waiting longer – say, 28 days – might not work as well, Dr. Appelbaum added. "Leukemic blasts are coming back by then and you may lose the opportunity to get that person transplanted when they need it," he said.

According to Dr. Appelbaum, identifying who will benefit most from transplant – and when – could be key to long-term success. "It offers a method that can potentially cure patients who can't be cured otherwise."



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