Getting to the Root of Leukemia

Researchers believe their greater understanding of leukemia stem cells will lead to more treatment options for people with the blood cancer.

January 9, 2019 By Garth Sundem

The day before Joel Rutstein planned to leave for a week-long trip to Hawaii with his wife, Barbara, and their grown children, an oncologist in Fort Collins gave Joel bad news.

In the course of his annual checkup, Joel's primary care physician had noticed a trend of declining hemoglobin in his blood. It was probably nothing. But after other tests couldn't explain the problem, Joel's doctor referred him to an oncologist for a bone marrow biopsy. It was the result of this biopsy that Joel learned that day before Hawaii.

"I said, Barbara, I think I just got a death sentence," Joel says. "The oncologist said it was very bad and that I probably wasn't going to live."

They went to Hawaii. Joel and Barbara agree that it was not their best vacation.

What Joel's biopsy showed was that he had a malignant condition called myelodysplastic syndrome, or MDS. In Joel's form of MDS, blood-forming cells in bone marrow had mutated so that instead of making healthy blood cells, they were making dangerous, immature blood cells, called blasts, which were accumulating in his blood. If Joel's bone marrow passed 20 percent blasts, he would technically no longer have MDS, he would have acute myeloid leukemia (AML).

For patients under age 60, treatment for AML includes chemotherapy and, if needed, bone marrow transplant. Patients over age 60 are often unable to withstand such aggressive treatment. Despite the fact that Joel is unusually fit — he swims most days at the noon-hour faculty and staff fitness program at Colorado State University, where he spent his career overseeing the library system — his age made him an imperfect candidate for treatment.

"When I was diagnosed, we heard about other people we know who had MDS," Joel says. "One of them was a woman my brother knew, whom we had met, who was living in the Boston area. She started getting chemotherapy. Her MDS morphed into leukemia and she eventually died."

The problem, even for younger patients, is that MDS and AML are conditions caused not just by cancer cells, but by cancer stem cells. And while chemotherapy kills run-of-the-mill cancer cells, it is almost completely useless against cancer stem cells. In fact, despite decades of research,

cancer stem cells remain about as easy to kill as goat head weed. And like a weed, even when chemotherapy is an option for AML, it often kills the bulk of the “plant” without killing the “root” — despite killing leukemia cells, unless you kill the leukemia stem cells, the disease will almost inevitably regrow.

Once Joel’s MDS progressed to AML, his prognosis would be poor, with survival likely measured in months. Thus his oncologist’s pessimism.

But what Joel and Barbara didn’t know at the time is that just down the I-25 on the Anschutz Medical Campus, a unique treatment program had grown up around groundbreaking research targeting these cancer stem cells that create MDS and eventually AML.

The Science of Leukemia Stem Cells

“People had been talking about the idea of leukemia stem cells (LSCs) since the 1950s. In the mid-1990s, they finally found them,” says Craig T. Jordan, PhD, investigator at CU Cancer Center, Chief of the Division of Hematology and the Nancy Carroll Allen Professor of Hematology at the CU School of Medicine.

At that time in the 90s, Jordan had recently completed school and training at Berkeley, Princeton, and M.I.T., and had just taken his first independent research position as an assistant professor at the University of Kentucky. His previous studies had been focused on normal blood-forming stem cells, called hematopoietic stem cells, or HSCs. As a new assistant professor, Jordan was intrigued by the challenge of LSCs, and shifted his research to focus on understanding and eradicating these cells.

What is an LSC? Think of it like an HSC with a pirate’s eye patch — if you can recognize the eye patch, you can distinguish beneficial HSCs from dangerous LSCs. In the year 2000, Jordan found it — an “eye patch” in the form of a cell-surface protein called CD123. LSCs coat themselves with CD123. HSCs don’t.

“That gave us the ability to separate normal HSCs from leukemia stem cells. Once you can separate them, you can study the differences between them,” Jordan says.

Jordan started looking for the LSC Achilles’ heel, not only a difference like CD123 that marked LSCs as distinct from HSCs, but a difference that LSCs needed to live — a difference that could be a target for drugs that would kill them. In fact, it turned out to be surprisingly easy to find differences between HSCs and LSCs. There were literally hundreds of them! The problem was that stem cells within one leukemia proved to be incredibly diverse, and there seemed to be no common difference.

“We found lots of things that were different and lots of ways to kill them, but few ways to kill all of them,” Jordan says. “If you kill 99 percent of the LSCs driving a leukemia, you can knock the disease down temporarily, but that little bit’s always going to grow back.”

To understand what he means, let's go back to our pirate. In addition to their eye patch, some pirates depend on a peg-leg. But others have hook hands. Sawing off the peg-leg does nothing against the pirates with hook hands. And attacking the hook-hands does nothing against the ones with peg-legs. It's the same with LSCs — targeting one weakness killed some cells, but not others. And when some LSCs survived, they were able to regrow the disease.

In order to attack all LSCs, Jordan needed to find the common weakness shared by all of these cells (and not also shared by the HSCs, which he didn't want to kill!). In a major contribution to the field of cancer research, Jordan found it.

"It turns out that the most common weakness of LSCs is how these cells make energy," Jordan says. "The way leukemia stem cells make energy is different than how normal stem cells make energy. And we found that a drug called venetoclax stops them from making energy in this way, without harming the mechanism that normal stem cells use to make energy."

With that discovery, Jordan had the science. Now he needed a doctor to help him deliver that science to patients who desperately needed it.

Doctors Enter Stage-Left

While Jordan was picking apart the science of LSCs, Daniel Pollyea was a hematology fellow at Stanford University.

"Fellows had to present journal articles at a weekly meeting, where faculty enjoyed grilling the presenter to ensure he/she understood the paper," Pollyea says. "When it was my turn, the paper I chose happened to be from the lab of Craig Jordan, describing a new therapy he was developing to target leukemia stem cells. Over the course of my preparation I learned that paper very well, and starting then, became fascinated with the biology of leukemia stem cells and the potential to target them in the clinic."

A few years later, Dr. Pollyea finished his fellowship and accepted a position as junior faculty at CU Cancer Center. He was closely followed by Clay Smith, MD, and established leader in the study of blood stem cells, who was recruited as program director of CU's Blood Cancer and Bone Marrow Transplant program. By 2013, with Smith and Pollyea in place, even a researcher of Craig Jordan's stature couldn't help but notice that a new kind of blood cancer program was coalescing in Colorado.

"There were a couple of important reasons I came to CU," Jordan says. "The first was the opportunity to build a program with Clay Smith, whom I had known for 20 years. The second big reason I chose CU was the opportunity to work with Dan Pollyea. It was clear from the first time we met that he would be a great partner in developing novel AML therapies.

"We immediately began to collaborate," Pollyea says, "and decided that the central theme of our leukemia program would be the study of leukemia stem cells and the clinical development of

targeted therapies to eradicate this population."

In the subsequent 5 years, what Jordan, Pollyea, and Smith have built together at the CU Cancer Center is a unique program targeting these cells at the root of blood cancers.

"We've had an extraordinary partnership," Jordan says. "Me in the lab, and Dan and Clay in the clinic. We live in each other's worlds as closely as we can. That's allowed us to do really deeply integrated research. We do things in the lab that are informed by the clinical problem, and then when things move into the clinic, we have an unprecedented level of depth with the patients."

Science Saves Lives

One of these patients is Joel Rutstein.

"In February 2016, we got blood count results back and everything was shot to hell," Joel says. "Normal blood cells had all dropped to practically zero. The MDS was morphing into leukemia."

His request for a second opinion brought him to CU Cancer Center, where Pollyea explained the options: They could treat Joel's leukemia with chemotherapy, but the stem cells that survived would likely restart the disease. Or Joel could take part in a new clinical trial open at CU and a few partner centers around the country, adding venetoclax to standard-of-care treatment.

For Joel, the choice was obvious. He started the trial.

First was a course of the commonly-used, low-intensity chemotherapy, azacitidine, to knock down the bulk of the cancer cells (even while killing the "root" of LSCs was the goal, why not also mow over the "weeds" of regular leukemia cells?). Along with chemotherapy, Joel took the drug venetoclax to block the leukemia stem cells' ability to make energy. After the short course of chemotherapy ended, Joel stayed on venetoclax.

"Blood counts recovered, blast counts went down. Eventually, by early fall, blood counts and even hemoglobin were back to normal," Joel says. His only side effect has been diarrhea a few times per month. "Since I can live a normal life with this drug, I don't have any interest in going off of it," he says.

Joel was not alone on the clinical trial. In all, there were 33 patients treated on this round of the trial. All were older than age 65 and ineligible for the extremely taxing chemotherapy that is used to treat AML in younger patients. Thus all 33 patients had very poor prognosis. In this group, 91 percent of patients achieved what Pollyea calls an "overall response," many of whom continue to be in durable remissions — which less careful people might be tempted to call a cure.

A New Paradigm for the Treatment of AML

Since the early 1970s, chemotherapy and sometimes bone marrow transplant have been the

standard-of-care for AML. The results have never been anywhere near perfect. And because the side effects of treatment itself are life-threatening, for older patients, even this imperfect treatment has been impossible. Now the basic science from Jordan's lab and the results from clinical trials in Pollyea's and Smith's patients are leading to a new paradigm for the treatment of AML — one that offers real hope for all patients.

And Jordan has groomed a new generation of scientists to lead this change. Just this fall, working in the Jordan lab, Courtney Jones, PhD, and Brett Stevens, PhD, were able to pinpoint the LSC's source of energy — instead of glucose, it turns out these cells depend on "burning" amino acids — and these young researchers were also able to show why ventoclax works: It stops the cells' ability to use amino acids for energy.

"The work to understand how amino acids fuel LSCs was only possible through a great collaborative effort," Jordan says. "Alongside our team's expertise in stem cells, we partnered with Dr. Angelo D'Alessandro, a leading expert on metabolism."

"We had previously shown that some alternate form of energy was important for LSCs and that ventoclax stopped their ability to use it," says Courtney Jones. "Now, after these studies, we were able to fill in that missing piece of the puzzle to implicate amino acids: LSCs need amino acid metabolism and venetoclax stops it." Their results are published in the journal Cancer Cell.

Meanwhile the Jordan lab's Brett Stevens, Courtney Jones, Amanda Winters, Shanshan Pei, and Mohammad Minhajuddin, had been backfilling our understanding of the science behind Joel Rutstein's clinical trial, showing that the clinical trial did, in fact, target LSCs in these patients, and that the trial accomplished this, as predicted, by nixing LSCs' energy metabolism.

"Patients' results showed that the trial was working, but we also needed to show why it was working — that it wasn't just some other effect of adding venetoclax to treatment. Our work shows that the reason patients improved is because we turned off LSC metabolism and specifically killed these cells," says Brett Stevens. Stevens's science is published along with the results of the clinical trial in the prestigious journal Nature Medicine.

Based on the very promising clinical trial results at CU, along with similar findings from several other cancer centers around the country, venetoclax is poised to receive FDA approval for the treatment of AML. More importantly, the science from Jordan's lab and the unique collaboration with Pollyea and Smith who believed in it promises to provide even better therapies for AML.

"There is still plenty of work to do for patients with AML," says Jordan. "Even though the early trials have shown major improvements, it's clear that not all patients are cured."

Now with a better understanding of LSCs in hand, Jordan and his collaborators are optimistic that they and scientists around the country will soon be able to provide even more options for patients with AML.

"When I was a fellow, I learned how to tell AML patients they were going to die," Pollyea says.

“Now I’m talking with my patients about their vacations and how their grandchildren are doing. It’s a fundamental change to the treatment of AML.”

As for Joel Rutstein, he says, “My story isn’t a real exciting one. There’s no car chase, no femme fatal. I don’t know why I happened to get diagnosed when I did or why this treatment happened to come around when it did. I just know that if I weren’t on this drug program, I wouldn’t be here.

This article was originally published on January 3, 2019, by the University of Colorado Cancer Center. It is republished with permission.

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