New Blood

By Tom Nugent

One summer morning in 1981, a 32-year-old assistant professor at The Johns Hopkins University School of Medicine sat at his kitchen table, doodling on a yellow legal pad. Between sips of coffee, the physician scribbled a series of phrases and images on the paper in front of him. Among the many words he wrote were three that would one day make him a legend in the world of cancer research: *marrow stem cells*. And among the many images he drew were a grinning fish and a dangling hook.

Curt Civin ’70 is a pediatric oncologist, and his doodling that day reflected his preoccupation with what was then the most challenging problem in his field: almost 80 percent of young leukemia patients were dying, even with bone-marrow transplants, because of marrow rejection and other treatment complications or cancer recurrence. Like many pediatric oncologists, Civin was looking for a way to give patients new blood that would be free of cancer cells and immune side effects. For Civin the quest had a special meaning.

A biology major at Amherst, Civin had always been keenly interested in medical research. Then, during his senior year, his mother died after a long fight with breast cancer. “All of a sudden,” he recalls today, “instead of looking vaguely at science and medicine on my horizon, I was looking specifically at cancer. The [medical] treatment my mother received was so primitive—so toxic and ineffective—that it made me realize how much we didn’t know about cancer. Month after month I watched her suffering terribly, and there was nothing I could do about it. I vowed that I would spend my career working on cancer.”

After graduating from Amherst, he attended Harvard Medical School and completed his residency in pediatrics at the Boston Children’s Hospital Medical Center. After additional training in immunology research and pediatric oncology at the National Institutes of Health, he signed on as a faculty physician-scientist in pediatric oncology at Johns Hopkins in 1979. Only two years later, while caring for dozens of young cancer patients every day, Civin began the long series of experiments and observations that eventually led to his breakthrough.

The problem that Civin was trying to solve was enormously difficult at the molecular level, but the clinical issues were nonetheless clear. Even with compatible donors, lymphocytes in the transplanted donor bone marrow would often attack the patient’s own tissues. To avoid that problem, doctors would sometimes turn to the patient’s own marrow. If it appeared that the patient’s marrow was cancer-free, doctors would remove and store it in a sophisticated freezer, give the patient high levels of chemotherapy (and sometimes radiotherapy) in an attempt to kill

the cancer, and then reintroduce the stored marrow to make new blood. But too often the patient's marrow contained a small number of cancer cells that would grow back and cause cancer recurrence.

Civin wondered if there were an immunological way to isolate the marrow's "master cells" (also known as "hematopoietic stem cells") that give birth to the new blood cells, and then inject those back into the patient, where they could begin building the new ingredients (white and red blood cells, along with platelets) required to repair the ravaged body's blood and immune systems. If he could isolate these stem cells, he could use them to boost healthy blood production, while reducing the risk of introducing cancer cells that contaminated the bone marrow.

Unfortunately for Civin and his fellow cancer researchers, only about 1 percent of the cells in human bone marrow belong to the stem-cell variety that can build different kinds of blood and immune cells from scratch. In 1981, there was no way to pull out these rare stem cells. Without a stem-cell-specific tool, the researchers had little hope of being able to isolate and then harvest the cells. Until that summer morning in 1981, the sheer complexity of this needle-in-a-haystack chemistry problem had defeated researchers.

Enter the fishhook and the nibbling fish.

Remembering that moment of insight during a recent interview in his lab at The Johns Hopkins University School of Medicine, Civin lit up with the fiery enthusiasm of a born researcher. "As I struggled with the problem," he recalled, "I gradually began to think of isolating the stem cell as catching a fish. And so I asked myself: 'What hook can I use to catch it?' I soon realized that if I could make a monoclonal antibody targeted to a specific antigen on the stem cell, that antibody would provide a hook to go in and 'catch' the 1 percent of bone-marrow blood cells that are actually stem cells."

Translation: What Civin wanted to do was build an antibody, a foreign-cell-attacking protein, that would recognize and then bind to an "antigen"—a signature protein molecule that would be found only on the stem cell.

If Civin and his fellow researchers at Hopkins could make the correct antibody, it would attach to an antigen contained only in the stem cell, and not to the remaining 99 percent of bone-marrow cells. The researchers would at last have their fishhook—a molecular tool that would allow them to isolate and extract stem cells by first binding them with the antibody and then removing them from the surrounding blood cells, especially the cancer cells.

So far, so good.

But was there such an antigen, unique to stem cells? And if it existed, how could Civin and his colleagues make their designer antibody without knowing the precise identity of this

antigen? For the endlessly doodling Civin, the answer came together slowly, over a period of more than a year. “Some of my best ideas come when I’m in the shower, or out in the back yard raking leaves,” he says, describing how the final piece of the stem-cell puzzle gradually emerged. “I think many research scientists would agree with me that when it comes to making new discoveries, creativity and imagination are far more important than mere factual knowledge.”

In the case of Civin’s stem-cell breakthrough, the solution to the antigen problem was remarkably simple and also rather daring. “Because I’d been working with leukemia patients day in and day out,” he says, “I knew a great deal about leukemia cells. For example, I knew that leukemia cells have been distorted by ‘arrested development.’ In some cases, leukemia cells appear to be ‘frozen’ at a primitive, stem-cell-like stage of development, probably because their destructively scrambled DNA programming keeps them from developing into mature cells.

“So with this thought in mind, I asked myself: If the leukemia cell is like a stem cell in so many ways, why not look for an antigen that might be present on a leukemia cell—and not on the many types of mature cells of the blood and immune systems? If we could identify such an antigen by making an antibody that would bind to it, and if the same antigen was indeed present on the stem cell, we would then be able to use the antibody to pull stem cells out of normal (or cancer-involved) marrow. The healthy stem cells would theoretically give us an endless supply of new blood cells that would not include any cancer cells.”

With his new screening strategy now worked out on paper, Civin proceeded to the next step in the plan: obtaining federal government funding for the huge, multiyear project. But the project was expensive, and the scientific panels that reviewed Civin’s grant proposals decided the odds against success were too great to risk investing several million dollars in the effort.

“That was very frustrating, very disappointing,” Civin says. “We needed the funds badly, but we couldn’t convince the panels that our testing system would actually work.” He pauses for a moment, and his eyes light up with merriment: “As usual, though, I managed to look on the bright side. Remember, I’m a pediatric oncologist. I take care of kids with cancer, so for me, the cup is always half full, even if it contains only a single drop. When they turned down all our funding applications, I just told myself: ‘Okay, they don’t really get it, and the good news is, we’re not going to have any competition in this area [of research] for the next few years.’”

Civin decided to fund the project with his own Johns Hopkins “start-up” lab budget and to run it on a financial shoestring. “It took us three years of nonstop effort to produce the monoclonal antibody that specifically identified stem cells,” he says with a smile of nostalgia. “And we were gambling all the way. In order for our screening strategy to work, several things had to go exactly right. And they did. By 1984, we had discovered that our antibody bound to an

antigen on stem cells but not mature blood cells or most types of cancer. We were very fortunate, but we also made some very good hypotheses along the way. Once we had our antibody, we could identify and isolate the stem cells we wanted. It took another decade of testing and improvement by the greater scientific community, of course, but the results were conclusive. Based on our doodles, we had managed to discover and develop a platform technology to identify and purify stem cells for research and for transplant into patients."

Former FDA commissioner David Kessler '73 (now dean of the University of California, San Francisco, Medical School) is convinced that Civin's discovery will go on benefiting cancer patients far into the future: "There's no question that Curt is a pioneer in stem-cell research, or that his contribution will have major implications in his field. What he accomplished through tireless effort and dedication will have an impact on both cancer research and treatment in the years ahead," Kessler says.

Adds best-selling author Tom Clancy, a long-time financial supporter of Civin's lab and a close personal friend: "Fighting cancer is no different from fighting any other war, and I regard Curt Civin as a hero of that conflict. He spent thousands of hours and made immense personal sacrifices in order to achieve this scientific breakthrough."

The influential Intellectual Property Owners Association in 1999 named Civin Inventor of the Year for creating the stem-cell technology, which was patented under the name CD34 and approved for general medical use by the U.S. Food and Drug Administration in 1996. He has received many other honors for his work, including the Oscar Schotte and Soma Weiss Awards at his Amherst graduation, the Leukemia Society of America Scholar Award, the Frederick and Bernadette Stohlman Award, the Kantor Family Prize for Cancer Research Excellence and the King Fahd Chair in Pediatric Oncology and the Herman & Walter Samuelson Chair in Cancer Research at Johns Hopkins. Civin says, however, that his most cherished citation came in 2001 from his alma mater. "I've been thrilled to receive many awards for my research," Civin says, "but it was almost overwhelming to receive an honorary degree from Amherst, the institution and people who launched me."

Today, Civin's stem-cell screening and transplant technology is used all around the world. "When I graduated from medical school we were losing 80 percent of the kids who got blood cancer, and today we're only losing about 20 percent," Civin says with a quiet smile. "I think every researcher enjoys making discoveries. But when those discoveries lead directly to helping patients—wow!"

Curt Civin today co-directs the Johns Hopkins Immunology & Hematopoiesis research division and also serves as editor of the influential journal *Stem Cells*. The author of hundreds of

scientific research papers and two books, he lectures frequently around the world on the tools he invented for bone-marrow transplant and stem-cell research in general. But his greatest passion is reserved for the children he watches over each day on the Hopkins pediatric-cancer ward.

"Treating children with cancer can be very challenging at times," he says quietly, when asked to describe his greatest accomplishment as a physician, "because you know you're going to lose one patient in five and probably sooner rather than later. But I never let myself become depressed at the death of a patient." Frowning a little, he shakes his head with sober determination. "Sure, there's a grieving process that goes on when you lose a child. But there are always other patients out there on the floor, and they're also relying on you. I can't afford to show them a long face. If I have to, I pause for a moment at the door, take a deep breath and then remind myself that I'm there to serve the living, not grieve endlessly for the dead. And when I push that door open and walk into a new patient's hospital room, you can be sure that I'll be cheerful and upbeat, ready to help that child as much as possible, to fight the very best fight I can."