By Tom Nugent

When Curt Civin '70 arrived on the Amherst campus in 1966, he was already a "huge fan of science and biology" with a keen interest in medical research. "Whenever I think about Amherst," says Civin today, "I remember the view from the old biology lab, looking out toward the Holyoke Range. In my memory, I'm standing there filling my test tubes, but my eyes are on the gorgeous view outside those windows. The campus was so beautiful, that it often seemed as if we were actually enjoying 'the life of the mind' in ancient Athens. I've visited a lot of university and college campuses over the years, but I don't think I've ever seen one with the physical beauty of Amherst."

But the golden days of Civin's undergraduate education were destined to end quickly. During his junior year at Amherst, his mother was diagnosed with breast cancer and quickly became ill. "All of a sudden," he recalls today, "instead of looking vaguely at science and medicine on my horizon, I was looking specifically at cancer. It was a very painful period in my life. 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."

During the fall of his senior year, the cancer took his mother's life. "I was driving back to campus from a medical school interview," he recalls, "and that was when she died. I learned about it when I got back to school, and I vowed that I would spend my career working on cancer. Somehow, I knew that this was what my mother would have wanted."

Not only did Civin pursue his vow to work on cancer, but he chose perhaps the most emotionally difficult aspect of cancer work: pediatric oncology. Civin went from Amherst to 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 the Johns Hopkins University School of Medicine in 1979. Only two years later, while caring for young cancer victims most days, he would begin the long series of plans and experiments that eventually led to a dramatic breakthrough in medicine.

It began one summer morning back in 1980, when the 31-year-old Civin sat at his kitchen table doodling on a yellow legal pad. Between sips of freshly brewed coffee, the youthful physician found himself scribbling a series of verbal phrases and cartoon images on the paper in front of him. Among the many words he wrote were three that would one day help make him famous in the world of cancer and blood research: marrow stem cells. Among the images he drew were a grinning fish and a dangling hook.

His doodling session was part of an ongoing effort to solve a major research problem relating to the cancers he was treating in his young patients. The clinical issue was clear. Bone marrow transplants using a donor's marrow often failed, or could not even be performed, because of immune-system incompatibilities between transplant recipient and potential donors. Thus, doctors were turning to using a 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 to kill the cancer, and then infuse the stored marrow. But too often the

patient's marrow contained a cancer cell(s) that could not be detected by the best tests, and then the cancer would grow back. Civin wondered if there were an immunological way to isolate the marrow's "master cells" (also know as "hematopoietic stem cells") that gave *birth* to the new blood cells, and then inject the isolated cancer-free stem cells back into the patient, where they could begin building the new ingredients (white and red blood cells, along with platelets) required to replace the ravaged body's blood and immune systems? If he could substantially purify these stem cells, he could transplant them to provide healthy blood cell production, while reducing the risk of simultaneously administering cancer cells that might be present at a low level in 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 "fish out" these rare stem cells they needed. Without a stem cell-specific "fish hook", they had little hope of being able to isolate and then harvest the rare stem cells.

Creativity: More Important Than Knowledge?

Until that summer morning in 1981, the sheer complexity of this needle-in-a-haystack chemistry problem had defeated researchers who tried to isolate stem cells.

Enter the fishhook and the nibbling fish.

Remembering that moment of insight during a recent interview in his Hopkins lab, Civin lit up with the fiery enthusiasm of the born researcher. "The problem," he recalled, "was as simple as catching a fish. But: 'What hook can I use to catch a stem cell but not any other type of cell?' If I could make a monoclonal antibody targeted to an antigen present **selectively** on the stem cell, that antibody would provide a special kind of hook, a hook designed 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, or cell-attacking protein, that would bind to an "antigen"—a characteristic, or "identity signature" protein molecule that might be found **only** on the stem cell. Antibodies are produced by the body's immune system to attack "foreign" proteins—antigens— of bacteria, viruses, etc., in order to fend off infectious diseases.

If Civin and his fellow researchers at Hopkins could somehow 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. Once that step had been achieved, the researcher would have his selective fish hook—a molecular tool that would allow him to isolate and extract stem cells by first hooking them with the antibody and then reeling them in 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 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 backyard raking leaves," explained the researcher, while describing how the final piece of the stem cell puzzle gradually emerged. "I think many research scientists would agree with me that creativity and imagination are far more important than factual knowledge, when it comes to making new discoveries."

In the case of Civin's stem-cell breakthrough, the solution to the antigen problem was remarkably simple, and innovative. "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, in some cases, leukemia cells closely resembled stem cells. That is, in some cases, the leukemia cells appeared to be 'frozen' at a primitive "stem cell-like" stage of development, probably because of mutations in their DNA.

"So with this in mind, I sat down and asked myself: Why not look for an antigen that might be present on a primitive "stem cell-like" leukemia cell—but not in the many types of mature cells of the blood and immune systems? We could attempt to identify such a target antigen by seeking to make an antibody that would bind to the stem cell-like leukemia cells but not to normal mature blood cells. Then, if the same antigen was, indeed, present on the normal stem cell, we would be able to fish the normal stem cell out of normal (and perhaps many cases of cancer-involved) marrow, using the antibody. The normal stem cells would give us an endless supply of new blood cells that would be depleted of any cancer cells. Although it is tough to explain, purified stem cells might also be utilized to deal with immune compatibility problems with transplants from donors."

With his strategy now worked out on paper, Civin proceeded to the next step in the plan, to obtain federal government funding for the large, multiyear project. But another roadblock quickly emerged, when the scientific panels that reviewed his 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 today. "We needed the funds badly, but we couldn't convince the panels that our strategy would actually work." He pauses for a moment, and his eyes light up with merriment: "Fortunately, 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 NIH turned down our funding application, 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 awhile."

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 over three years of ferocious 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 strategy to work, several things had to go exactly right. By 1984, we had discovered that our antibody bound to an antigen (now known as CD34) on stem cells but not mature cells. We were very fortunate that we had made some very good predictions, 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 and thoughts of fishing, we had managed to discover and develop a platform technology to identify and purify stem cells for research and for transplant into patients."

Civin was "deeply thrilled" when the influential Intellectual Property Owners Association (IPOA) in 1999 named him Inventor of the Year for creating the stem-cell technology, which was patented and approved for general medical use by the U.S. Food and Drug Administration (FDA) in 1996.

Like the IPOA, former FDA commissioner and currently University of California, San Francisco Medical School Dean David Kessler '73 is convinced that Civin's discovery will go on benefiting cancer patients far down 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."

Adds best-selling author Tom Clancy, a longtime 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."

As of 2004, the medical record shows that Clancy isn't exaggerating in the least. By the first years of the new millennium, Civin's stem-cell screening and transplant technology was being used all around the world in over 10 thousand research papers, and to count and purify stem cells in thousands

of patients. "I think every researcher enjoys making discoveries. But when those discoveries lead directly to helping patients—wow!"

To illustrate his point, the now famous Fishhook Strategist quotes a well-known statement by everyone's great medical hero, Louis Pasteur: "To him who devotes his life to science, nothing can give more happiness than increasing the number of discoveries. But his cup of joy is full when the results of his studies immediately find practical applications."

Curt Civin today directs a major U.S. stem-cell laboratory 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. On their travels, Curt and his wife, Nancy (Smith College 1970: they met at a mixer sophomore year of college) like to try many new foods and restaurants, and consequently, Curt and Nancy work out together to keep near their Amherst-Smith College weights. Curt and Nancy continue to be amazed and thrilled by their accomplished sons, Josh (29) and Marc (27). I was 0 for 2 in recruiting them to Amherst, but they've done beautifully anyway. Josh graduated from Yale in 1996, then pursued a PhD in History at Oxford on a Rhodes Scholarship, followed by a Yale law degree in 2003. He's now clerking for the US Court of Appeals in Los Angeles, and engaged to an outstanding Yale Law School classmate (Katherine Tang Newberger, also about to start a US Court of Appeals clerkship). Younger son, Marc, graduated from Brown in 1999 and is an artist, painting the next great new art in San Francisco (Check him out on the wweb). So Curt and Nancy are taking every chance they can to travel to California this year.

Another major passion is the "adopted" children Civin watches over each day on the Hopkins pediatric cancer ward."Treating children with cancer can be very challenging at times," he says quietly, "because you know you're going to lose patients, some sooner than later. But I never let myself become pathologically depressed at the death of patient." Frowning a little, he shakes his head with sober determination. "Sure, there's a grieving process that goes on, when I lose a child. But it usually doesn't last too long, because there are always other patients out there on the floor, and they're also relying on me. I can't hurt them by showing them a really long face. (Although he does not claim this as a result of his own research, Civin's work-life has also been improved by the greatly reduced childhood fatality-rate for blood cancers such as leukemia and lymphoma s. "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.)

"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 to indulge my own grief 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 upbeat, ready to fight the very best fight I can, to help that child as much as possible."