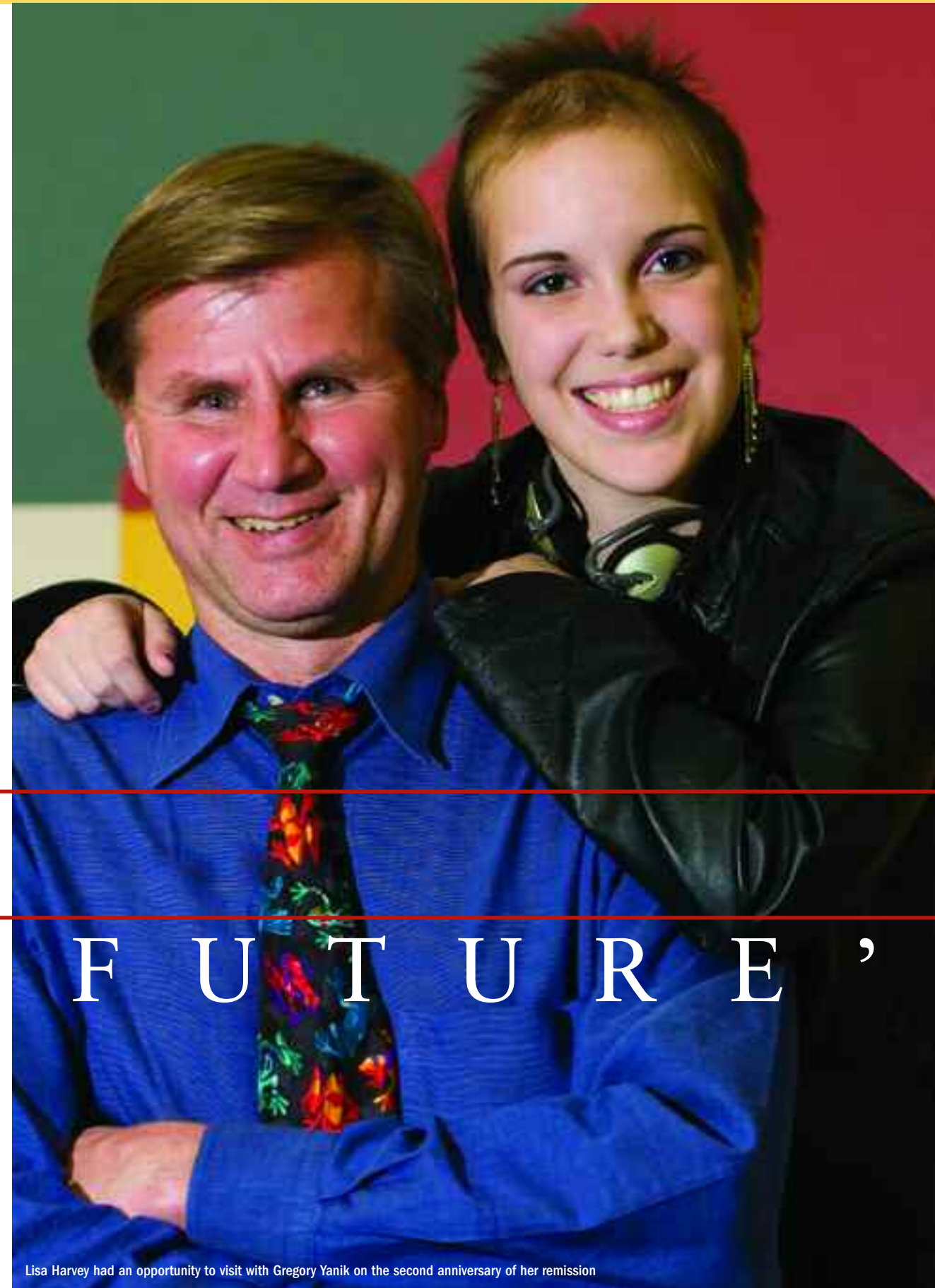


Lisa Harvey is an outgoing 16-year-old from Chelsea, Michigan, with a megawatt smile and a contagious enthusiasm for life. Petite and pretty, smart and self-confident, she bubbles over with news about her friends, her family, her summer vacation and that most precious symbol of teen-age independence — a new driver's license.

Blessed with a loving family, close friends and the ability to talk anytime to anybody about anything, Lisa is one of those young people who just seems destined to succeed, regardless of what the future may bring.

But two years ago, Lisa Harvey and her parents weren't sure she even had a future. Just as she was beginning her freshman year at Chelsea High School, doctors broke the news that Lisa's leukemia had returned. Chemotherapy hadn't worked and her only option was a bone marrow transplant.

"It's tough enough being diagnosed with cancer, but it's even harder to be told the cancer has come back," says Gregory A. Yanik, M.D., clinical associate professor of pediatrics in the U-M Blood and Marrow Transplant Program, who was one of the physicians on Lisa's health care team. "Because when the cancer comes back, it comes back in a tougher, bigger, more resistant form." ▶



Lisa Harvey had an opportunity to visit with Gregory Yanik on the second anniversary of her remission

'A BRIDGE TO THE FUTURE'

CLINIC MEETS LAB AS TRANSLATIONAL RESEARCH ADVANCES BLOOD AND MARROW TRANSPLANT SUCCESS AT MICHIGAN

According to Yanik, cancer patients like Lisa who come to the U-M for a blood or marrow transplant are typically those who have failed standard therapy, have types of cancer that are especially hard to treat, or have medical complications that make treatment more difficult and risky.

Lisa's transplant was one of about 250 performed each year by physicians in the Blood and Marrow Transplant Program. Part of the U-M Comprehensive Cancer Center, it is one of the largest transplant programs in the United States.

"We are developing a reputation as a place on the cutting-edge of transplant research," Yanik says. "We have some of the best physicians and nurses of any transplant program in the country. And this is fortunate, because we get the toughest cases."

"Over the last 10 years, we've seen major advances in the field of blood and marrow transplantation," says John E. Levine, M.D., associate professor of pediatrics and clinical director of the

WHEN CURE BECOMES KILLER

Although research advances have made bone marrow transplants much safer and more effective than they used to be, the side effects can still be extremely serious. Even after patients recover and seem to be doing well, many face a high risk of developing a common, and often deadly, post-transplant complication called graft-versus-host disease. In GVHD, transplanted immune cells from the donor (called the graft) attack the patient's skin, liver and gastrointestinal cells, triggering a massive inflammatory reaction that can kill the patient.

"Giving transplanted blood or marrow cells from another person to cancer patients is a form of immunotherapy called the graft-versus-leukemia effect," says James L.M. Ferrara, M.D., a professor of pediatrics and director of the Blood and Marrow Transplant Program. "New immune cells from the donor track down malignant cells in the patient and destroy them. Without the graft-ver-

joints, dry eyes, loss of appetite and fatigue. Sometimes the symptoms are mild and easy to treat. But, in severe cases, the effects of chronic GVHD can be life-altering.

Ferrara has spent much of his research career searching for the cause of graft-versus-host disease. After years of research with mice, Ferrara and his research team discovered that the disease attacks the patient's cells with a barrage of immune system proteins called inflammatory cytokines.

In research conducted with Kenneth Cooke, M.D., assistant professor of pediatrics in the Medical School, Ferrara identified a handful of likely suspects as being the trigger for this cytokine storm — especially an immune system protein called tumor necrosis factor.

"There's a drug called etanercept, or Enbrel, which was approved by the Food and Drug Administration to treat the inflammation and pain of severe arthritis," Ferrara says. "It works by blocking tumor necrosis factor, the same

"NEW THERAPIES AND DRUGS MAKE IT POSSIBLE FOR US TO TAKE MUCH SICKER PATIENTS, AND INFECTIONS THAT WERE A DEATH SENTENCE BEFORE ARE NOW HIGHLY TREATABLE. BUT THERE'S STILL AN UNACCEPTABLY HIGH FAILURE RATE."

—JOHN LEVINE

Pediatric Blood and Marrow Transplant Program. "We now lose fewer patients during the first month after transplant. New therapies and drugs make it possible for us to take much sicker patients, and infections that were a death sentence before are now highly treatable.

"But there's still an unacceptably high failure rate," Levine adds. "In many types of transplants, the mortality rate within three years is as high as 50 percent. Graft-versus-host disease is a big part of the problem."

sus-leukemia effect, the cancer usually comes back.

"Unfortunately, the donor's immune cells don't always distinguish between malignant and normal cells in the patient, and they can start attacking normal tissue," Ferrara adds. "When this happens, it's called graft-versus-host disease."

Patients who survive acute graft-versus-host disease often develop the chronic form of the disease. According to Levine, chronic GVHD can cause disfiguring and painful changes in the skin, damaged

protein we identified as a major cause of tissue damage associated with GVHD."

When the U-M research team tested the drug in laboratory mice and in a small group of patients, they discovered that it appeared to stop the deadly progression of graft-versus-host disease.

Based on extensive laboratory work and initial positive results in a small clinical study, U-M researchers have obtained funding from the FDA and the National Institutes of Health for two new clinical trials with etanercept.



JOHN LEVINE



JAMES FERRARA



KENNETH COOKE

One study will evaluate the effectiveness of giving etanercept to patients with GVHD, in addition to the traditional steroid drugs they receive to suppress their immune response. The second study will determine whether etanercept can prevent GVHD in high-risk patients after a bone marrow transplant from an unrelated donor.

"When we looked to see if laboratory observations in animals held true in humans, we found we could almost predict who will have post-transplant complications by measuring the amount of TNF-receptor protein in the patient's bloodstream," says Levine. "Patients with the lowest levels of TNF-receptor soon after the transplant have about a 40 percent chance of developing GVHD or other major complications. Those with the highest levels of this protein have an 80 percent chance."

There's also a direct connection between patient survival and levels of tumor necrosis factor receptor, according to Levine. Patients with high levels of TNF-receptor are twice as likely to die within three months after the transplant than those with low levels of the protein.

"Our goal in the prevention study, which is unique to the U-M, is to prevent graft-versus-host disease, or at least its most

serious effects, by blocking tumor necrosis factor with etanercept," Levine says.

"When we started to study GVHD in the laboratory, it was a complete black box," Ferrara says. "Now, just 10 years later, we are beginning clinical trials with etanercept. It's a great example of translational research and how it can transform how we care for patients."

THE POWER OF TRANSLATIONAL RESEARCH

Few areas of medicine have benefited more from translational research than blood and marrow transplantation. Bone marrow transplants were first developed in the 1950s to treat a rare disease called aplastic anemia. Since then, bone marrow transplants and peripheral blood stem cell transplants have cured thousands of children and adults with cancers of the blood and bone marrow, especially leukemia, lymphoma and multiple myeloma.

"These are treatments we couldn't do at all 40 years ago," Ferrara says. "Thirty years ago, we were just starting to do them and most patients died from the side effects. Although they are still seri-

ous procedures, advances through translational research have made them safer, more effective and an option for more cancer patients."

Translational research takes discoveries from the laboratory and brings the most promising to the clinic where they can be tested in patients. Results from clinical studies then go back to the laboratory to determine why they did or didn't work. The goal is to get new medical treatments developed, tested and on the market as quickly as possible.

"There's a lot of basic science taking place that will probably lead to medical breakthroughs one day," Levine says. "But we're interested in a breakthrough next week."

Many academic medical centers are interested in translational research, but few actually do it, according to Levine. It requires teamwork, planning and close working relationships between laboratory scientists and clinicians — things that don't occur naturally in the typical competitive university environment.

"There's always been a lot of clinical research and a lot of laboratory research, but the integration has only been done at a few centers," Levine says. "Michigan is one of them." ➤

"It's unusual to have this level of collaboration between scientists and clinicians," says Pavan R. Reddy, M.D., an assistant professor of internal medicine who joined the U-M faculty in 2002. "We work together to develop clinical research protocols based on what we've learned in the laboratory. Writing the protocol together helps minimize the chances of failure, which often happens when people get excited about something they see in the lab and rush it to clinic without working out the basic mechanism in detail."

"Some people say research is incompatible with quality patient care," says Ken Cooke. "But the truth is that research is *part of* outstanding patient care. Without clinical investigation, there's no way to learn how to minimize side effects and

make medical advances. This is the University of Michigan. At a place like this, we should be focused on raising the standard of care."

MAKING TRANSPLANTS SAFER

It doesn't look much different than an ordinary blood transfusion. But to someone with cancer, a blood or marrow transplant can mean a fresh supply of healthy blood cells, a new immune system and a second chance at life.

Primitive cells called hematopoietic stem cells are the secret to successful transplants. They develop into oxygen-carry-

ing red blood cells and all the different types of specialized white blood cells in the human immune system. Without them, there is no way for the body to replace old, worn-out blood and immune cells.

This can be a deadly problem for patients with leukemia and other types of cancer, because the intense chemotherapy and radiation they need to kill the cancer also destroys their blood-forming stem cells.

Hematopoietic stem cells like to hang out in bone marrow — the spongy, honeycombed tissue inside the breastbone and hip bones where new blood cells are produced. To obtain stem cells for a bone marrow transplant, doctors use a large needle to remove cells from marrow-filled cavities in the hip bone. Another option is a procedure called a peripheral blood stem cell transplant, in which physicians give drugs to make stem cells leave the bone marrow and enter the bloodstream, where they can be filtered out and collected in a process called apheresis.

"An autologous transplant uses stem cells from the patient's body, usually taken from the patient's blood," Ferrara says. "An allogeneic transplant uses stem cells from someone other than the patient or the patient's identical twin. Stem cells for allogeneic transplants most often come from donated bone marrow or umbilical cord blood. Whatever their source, stem cells are given to the patient through a central venous catheter that goes into the bloodstream. When the stem cells enter the patient's bone marrow, they settle in and start producing new blood and immune cells."

The greatest danger of complication occurs after allogeneic transplants, especially from an unrelated donor, because the risk of GVHD and other conditions involving an immune reaction between donor and host cells is especially high.

Until recently, the intense chemotherapy and radiation used to destroy a patient's cancer-infested bone marrow, and the associated risk of GVHD, made life-saving bone marrow transplants too

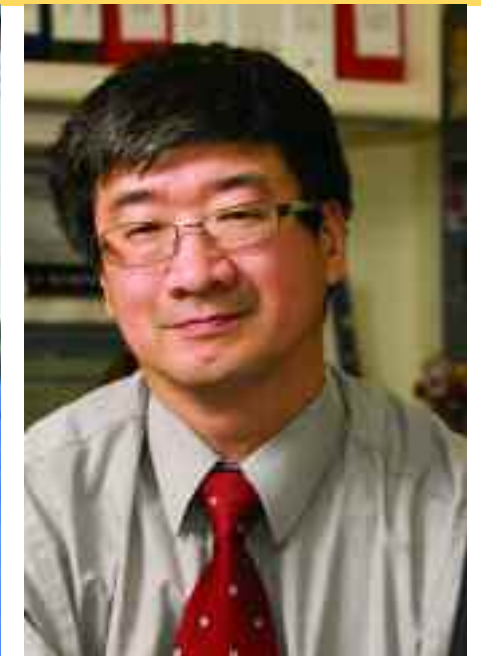
dangerous for older adults with cancer, who often have other health problems and are less able to tolerate the treatment's side effects.

"This is particularly true for adults age 55 and older," says Shin Mineishi, M.D., associate professor of internal medicine and clinical director of the U-M Adult Blood and Marrow Transplant Program. "Ironically, people over age 55 are the ones most likely to develop cancers that respond well to transplant treatment."

During the last 10 years, researchers have developed a new transplant preconditioning procedure, which uses much lower doses of chemotherapy than the standard full-intensity regimen. According to Mineishi, reduced intensity conditioning has revolutionized cancer



PAVAN REDDY



SHIN MINEISHI

"I BELIEVE STRONGLY THAT THE BEST CLINICAL CARE GOES HAND-IN-HAND WITH THE BEST RESEARCH. WE HAVE TO OFFER SOMETHING NEW OR BETTER THAN STANDARD TO EVERY PATIENT."

— SHIN MINEISHI



Peggy Parker (clinical care coordinator), Carol McMahon (research nurse), Diane Klann (clinical nurse III), Maria Kirk (clinical nurse I), Dawn Jones (research nurse), Shelli Anuszkiewicz (clinical care coordinator), Kim Kyro (clinical care coordinator), Maureen Rose (clinical nurse III)

Nurses and clinical care coordinators are vital members of the BMT team. Clinical nurses provide patients and their families with care and education about symptom management. Research nurses coordinate and implement specialized cancer research protocols by identifying patients eligible for clinical trials and ensuring the well-being of clinical trial patients throughout their care. Clinical care coordinators provide functional supervision of clerical staff, direct and support the BMT team through consultation with nurses and other team members, and ensure continuity and coordination in the inpatient and ambulatory care settings.

treatment for adults by making it possible for more adults with cancer, even those up to age 70, to receive a life-saving allogeneic transplant. As a result, about 200 of the 250 transplants performed at the U-M Cancer Center last year were for adults.

"We used to think it was high-dose chemotherapy that destroyed the cancer cells," Mineishi says. "Now we think it is the graft-versus-leukemia effect, or T cells from the donor's bone marrow, which attack and destroy the cancer cells. So it's not necessary to completely destroy the old bone marrow. You just need a little bit of chemotherapy and immune suppression to facilitate the engraftment of the donor cells."

Like many things involving cell transplant therapy, however, there's a trade-

off, according to Mineishi. Lower doses of chemotherapy mean more cancer cells escape the initial conditioning assault, leaving more cells for the patient's transplanted immune system to track down and destroy. If the remaining cancer cells reproduce faster than the new immune system can kill them, the cancer will return.

"Right now, we are doing about 70 percent full-intensity transplants and about 30 percent low-intensity," Mineishi says. "But it remains to be shown whether reduced intensity is as good as a full-intensity transplant. We need more clinical trials to determine the safest and most effective way to do transplants from unrelated donors in older patients. Our goal is to create the standard for innovative, scientific clinical trials designed to resolve these questions."

TRANSPLANTS IN THE FUTURE

In addition to helping older patients with cancer, research in the Blood and Marrow Transplant Program is improving survival rates for children with neuroblastoma — a cancer that develops in nerve cells in the abdomen or chest. Even with intense chemotherapy followed by a bone marrow transplant, only 30 percent of children diagnosed with neuroblastoma survive.

Over two decades ago, U-M scientists invented a compound called MIBG, which binds to substances produced by neuroblastoma cells. Originally, MIBG was used as a diagnostic imaging agent to help physicians see neuroblastoma tumors in X-ray type images. Several years ago, U-M scientists discovered that attaching ➤

A DAY UNLIKE ANY OTHER

a radioactive isotope called iodine-131 to MIBG made it possible to deliver the radiation directly inside the tumor.

“We are the lead institution for several national clinical trials to test MIBG therapy in children with refractory disease,” Yanik says. “We are testing it as a single-agent therapy, as well as with chemotherapy and a bone marrow transplant. The results are very promising.”

Yanik sees MIBG therapy as an example of future advances in cancer treatment that will, eventually, make bone marrow transplants obsolete. “One hundred years from now, we won’t be doing any bone marrow transplants,” he says. “Instead, we will have therapies that won’t require the high-dose chemotherapy or radiation we currently use, because they will be targeted at a specific tumor or gene defect.”

“I believe strongly that the best clinical care goes hand-in-hand with the best research,” Mineishi adds. “We have to offer something new or better than standard to every patient.”

As an example of how translational research can transform clinical care, Mineishi cites new applications for autologous blood stem cell transplants in treating other medical conditions, in addition to cancer. He says it was about 10 years ago when researchers first noticed that cancer patients with autoimmune diseases like scleroderma, lupus or rheumatoid arthritis sometimes experienced a remission or improvement after receiving a transplant to treat their cancer.

“The early research results were encouraging, because the transplant induced a remission in many autoimmune patients,” Mineishi says. “But it was also discouraging, because many patients relapsed.”

Since then, researchers have found that removing immune cells called T cells from the patient’s blood before returning stem cells to the patient helps prevent a relapse.

Early clinical studies in small groups of people with autoimmune disease were conducted at research institutions worldwide, including the U-M Health System. Results were so promising that the National Institutes of Health is now sponsoring a nationwide clinical trial to test the effectiveness of autologous stem

cell transplants against standard therapy in over 200 patients with the most severe form of scleroderma — an autoimmune disease that causes thickening and hardening of the skin, blood vessels and internal organs.

The U-M is one of 10 research institutions participating in the study. Mineishi is a co-investigator, along with James R. Seibold, M.D., U-M professor of internal medicine and an expert on the treatment of the disease. They hope to begin enrolling patients early in 2006.

“It’s like resetting the immune system to zero and starting all over again,” Mineishi explains. “We hope the patient will develop a normal immune system that will not attack his or her body anymore.”

Thanks to translational research, a procedure developed in the 1950s to treat one rare disease may have more applications than its inventors ever dreamed of. Today, scientists are exploring the possibility of using stem cell transplants to treat heart disease, regenerate damaged blood vessels and muscles, or even to prevent rejection of transplanted organs.

It’s an example of the power of this type of research, which Ferrara likes to call “a bridge to the future.”

“It’s not discovery at the same level as basic science,” Ferrara says. “It’s about the application of new ideas, techniques and perspectives to old problems. The whole point of translational research is to make the procedure better and safer through advances in multiple areas. To succeed, it requires scientific insights, energy, creativity, teamwork and a sustained institutional commitment. It’s what academic medicine does best: We create the new standards of clinical care.”

For patients like Lisa Harvey, two years out from her bone marrow transplant, doing well and looking toward a future filled with promise and potential, those new standards of care can make all the difference in the world. [m](#)

For additional information about Blood and Marrow Transplant Program researchers and their work, visit www.medicineatmichigan.org/magazine and follow the link at the end of this article.

Sick as she was, weak as she was, 14-year-old Lisa Harvey sat up in her hospital bed and typed these words into her Web log:

“November 10, 2003: The day started off slow, as an IV machine went off beeping and waking me up. The day was just the same as any other day I spent in the hospital. Just lying in bed trying to sleep away all that’s going on, trying not to let anything sink into my brain ... Slept more, got woken up for a shower. Went back to bed, tired and weary. Another day ... just another day. I get the drugs, everyone anxious. I didn’t really think much. I just laid there, waiting. Not thinking. It’s here. The huge bag of blood and marrow. Just a simple step and it’s dripping through the tubes into my blood. I think to myself, this day isn’t like any other day. This is the day someone saved my life.”

Before August of 2002, Harvey was just a typical, happy, healthy 13-year-old from Chelsea, Michigan. But that summer, she came home from camp looking different. Her mother, Nancy Harvey, recalls, “Her coloring was a little off, and she had bruising and swollen gums. I went online and searched ‘anemia’ first. But something made me look under ‘leukemia,’ too, and when I read that swollen gums were a symptom, I called the doctor and said, ‘I want blood work done, stat.’” Lisa went to the doctor on August 28 and was admitted to C.S. Mott Children’s Hospital that night. The diagnosis: adult leukemia. She had been in eighth grade for three days.

“Your world changes in a heartbeat,” says Nancy Harvey. “Nothing’s normal again. ‘Normal’ was August 27, 2002. August 28 was no longer normal.”

Four months of aggressive chemotherapy put Lisa’s cancer into remission, and the family let down their guard. But by August 2003, her blood counts were dropping rapidly. Lisa’s doctor, Jim Williams (who has since moved to Phoenix) had tears in his eyes as he told the stunned family Lisa had relapsed. Nancy Harvey says, “We were devastated. She was just starting to get her life back and I was not prepared. She didn’t



LISA AND NANCY HARVEY

look sick anymore; her hair had come back in beautifully. I just thought she’d beat it with chemo alone. Plus, Lisa has a certain chromosome that upped her survival rate to 80 percent, but she ended up being the first of the kids on the floor to relapse ... ”

The next step: a bone marrow transplant. Lisa is adopted, which made the search for a compatible donor more challenging. Her family, two biological half-sisters and friends all were checked, but no one came close. But the National Marrow Donor Program Registry had good news: a donor with 10 out of 10 points.

This time, the chemo leading up to the transplant was intense, painful and lonely for the bright and popular teenager. She spent months in the hospital, unable to see her friends or even go outside for fresh air. Then followed the transplant itself: the blood and marrow of a stranger entering her body and immediately setting to work to kill off the cancerous cells.

As for graft-versus-host disease, the most perilous complication of BMT, it simply never happened. Today, Lisa prides herself on her almost uncanny awareness of her body. “They told me, ‘You’re proba-

bly going to get graft-versus-host disease.’ And I said, ‘Uh, no — I’m *not* gonna get it.’ Then a half-year out, they said, ‘Well, you might still get it ...’ and I said, ‘I told you: I’m *not* gonna get it!’” A year later with no sign of GVHD, Lisa slyly told her doctors, “I told you so!”

After a year had passed since her transplant — the prescribed waiting period before donors and recipients contact each other — Lisa received a call from a young woman named Angie, a Head Start teacher from Tennessee who had donated the bone marrow Lisa received. In June, the Harveys — and a television crew — were at Detroit Metro Airport to greet Angie as she arrived for a six-day visit. Together, Lisa and Angie cut the ribbon for the local Relay for Life race, and participated in the run.

Today, Lisa is 16 years old. At camp this summer, she studied printing, drawing, mosaics and ceramics intensively. She is enjoying a normal year in high school. And she says the experience of her illness has changed her deeply.

“I’ve learned how to listen to my body really well,” she says. “I’ve learned to believe that everything happens for a reason, and that my cancer happened to me so that I could learn how to handle life better. I definitely became more patient and so much more observant. I remember once, after isolation, on the ride home I was in awe of how everything looked. I remembered it all, but it was so much more precious.”

Lisa says that despite lacking some physical endurance and experiencing some lingering “hair issues,” she feels great — and an almost inexpressible gratitude to her donor. “There really are no words,” she says. “It’s sort of crazy — Angie has seasonal allergies and she gave them to me! Thanks a lot, Angie!” she jokes. Then she pauses and adds, “It’s just a neat thing. Instead of one person, you’re like two. In a way, it’s quite symbolic of the whole process of someone saving your life and always being a part of you ... ” [m](#)

—by Whitley Hill