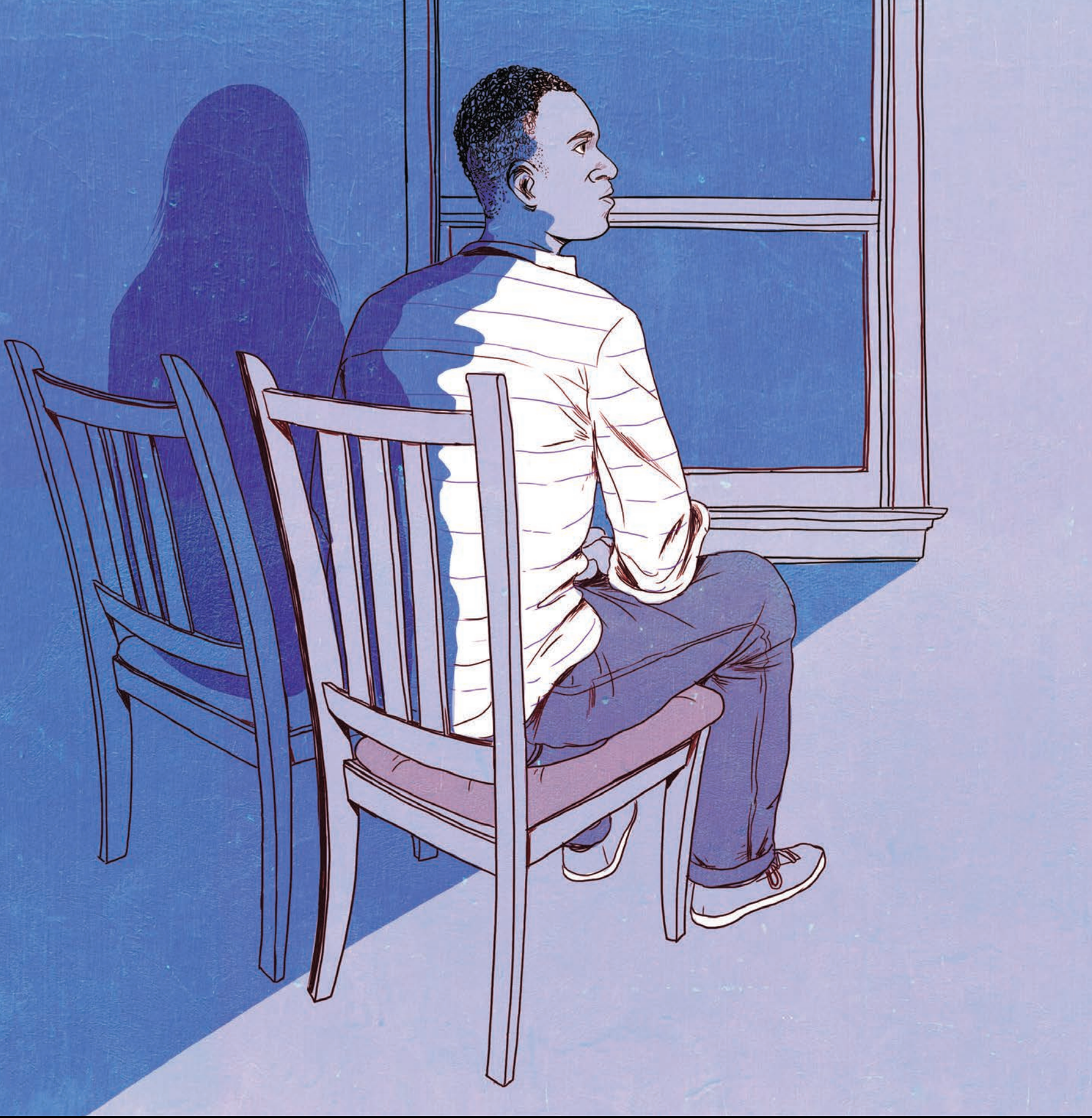

**A new combined lung/bone marrow transplant is saving the lives of some very sick patients. Not only that, but when successful, these patients are gaining the immune systems of the donors, so they can lead lives free of immunosuppressant drugs.**

# BEYOND THE DONOR MATCH

## WHEN ONE PERSON BECOMES PART OF THE OTHER

BY SHARON TREGASKIS

Among the mementos in the Rangos Research Center office of pediatrician Paul Szabolcs hangs a front-page news story published in 2010. In the accompanying photo, confetti showers down on a slight 16-year-old as health care providers and fellow patients celebrate her release from the local bone marrow transplantation unit.

When they met in 2009, Szabolcs recalls, the flaxen-haired youngster was in a precipitous decline. At just 4'5" and 48 pounds, Daphne (we've changed patient names in this story) required intravenous nutrition and high-flow oxygen supplementation; her muscles were so depleted she could no longer walk independently. Diagnosed as an infant with the same hereditary immune deficiency that had killed her older brother before his fourth birthday, she had endured recurrent respiratory infections for six years. Still, she acted in local theatre productions, excelled in her Advanced Placement courses, earned her driver's permit. When she couldn't attend school in person, she participated by Skype.

A transplant of stem cell–rich cord blood, Szabolcs's specialty, could replace Daphne's delicate immune system with one vigorous enough to protect her lungs. But she was too weak to endure the radiation and chemotherapy that precedes such transplants. And those persistent respiratory

ILLUSTARATIONS | MICHAEL HIRSHON

infections had inflicted such extensive damage, a new set of lungs was equally imperative—and risky. The drugs used to prevent organ rejection would only accelerate her immune decline. "It would have been futile and irresponsible to offer any kind of [conventional] transplant," says Szabolcs. "We would have killed her."

Together with her pulmonologist, Szabolcs—now chief of the Division of Blood and Marrow Transplantation and Cellular Therapies at UPMC Children's Hospital of Pittsburgh—proposed a novel solution, then garnered the myriad institutional and federal approvals required to proceed. Her doctors would seek a single deceased donor to furnish both bone marrow and lungs. If their scheme worked, Daphne would be cured of her hereditary immune dysfunction and spared the side effects caused by lifelong use of the medications necessary to prevent rejection.

The procedure they envisioned would take months. If a size- and tissue-matched donor could be identified in time, the marrow would be harvested and processed to deplete the most immunologically aggressive cells, then frozen. The lungs would be transplanted immediately. If Daphne survived that surgery, she would spend a few months on immunosuppressants while regaining her strength, then proceed with chemotherapy, radiation, and finally transplantation of the cryopreserved bone marrow.

"Quitting was not her nature," says Szabolcs. "So I felt that it was my obligation to come up with a plan that, while without precedent, still carried hope."

By the time Szabolcs and his colleagues reported on the case in a 2014 letter to the *Journal of Allergy and Clinical Immunology*, their former patient was attending college on a full scholarship and giving campus walking tours. This fall she'll commence graduate studies in computational analysis and public policy. And for eight years and counting, her own cells and those of her donor have coexisted in harmony, without the aid of immunosuppressant therapy.

Clinicians refer to that outcome as "immunological tolerance," and it's been commonplace in bone marrow transplantation since the procedure was pioneered in the 1950s. In the field of lung transplantation, however, Daphne's experience is the stuff of fantasy. Among those who live a full decade after receiving their new lungs, 75 percent experience chronic rejection. And they're the lucky ones—45 percent of recipients die within the first five years of their transplant surgery.

"This equates to the prognosis of a moderate cancer, and it's supposed to be a life-saving transplant," says associate professor of medicine John F. McDyer, director of Pitt's Lung Transplantation Translational Research Program. "There's a lot of room for improvement."

It's no surprise that of all the solid organs, lung transplants are the most difficult to manage, says Mark Gladwin, the Jack D. Myers Professor, chair of the Department of Medicine, and director of the Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute.

"The lungs are always exposed to viral and bacterial infections, which stimulate inflammation and increase the risk of activating the immune system. The activated immune system will also attack the donor's lung in a process called rejection," he says. "The idea of combining the bone marrow from the donor with the lungs from the same donor could be a breakthrough by eliminating the risk of the bone marrow attacking the lungs."

Like Szabolcs, McDyer joined the Pitt faculty in 2011—recruited by Gladwin. And soon after they met, the two started laying the groundwork for a joint clinical and research program to continue the work Szabolcs began in 2009. They teamed up with Jonathan D'Cunha, Pitt's surgical director of adult lung transplant, and expanded the effort to include more adults plagued with both lung and bone marrow failures—people with idiopathic pulmonary fibrosis, sickle cell, scleroderma, and a condition McDyer has studied extensively known as short telomere syndrome. So far, their program has garnered more than $12 million in combined funds from the National Institutes of Health and UPMC. Already, they've enrolled 10 patients and performed five combined lung and bone marrow transplants.

Bone marrow transplantation was pioneered in the 1950s as a curative treatment for leukemia, in which cancer emerges within the bone marrow. First, doctors blast the patient's leukemic cells with radiation and chemotherapy (what's called myeloablative conditioning); then they replace the immune system they obliterated with donor marrow. When the donor marrow starts cranking out red and white blood cells, a state clinically known as engraftment, the transplant is considered a success. In the early years, only identical twins were eligible to receive transplants. In time, it became obvious that absent a twin, more distant matches were sufficient—and far more widely available. It also became obvious that the myeloablative regimen necessary to kill every leukemic cell lingering in the marrow posed significant hazards. Even today, says Szabolcs, the regimen kills one in 10 or more patients.

**"When she started getting sicker and sicker, there was a part of me that started trying to prepare myself for a life without her. It's amazing that she's here."**

Whether the patient has leukemia or is about to undergo a novel combined lung and bone marrow transplant, the trick is finding the delicate balance where a patient survives both conditioning and the physiological chaos that can ensue when host and donor immunology clash. "When you don't have to kill every last leukemic cell [for instance], you want to dial back the intensity of the conditioning," says Szabolcs. "But there's a possibility the patient's stem cells may recover."

That's what happened in 2016, when Szabolcs and McDyer did their first lung and bone marrow transplant at Pitt. Madeline was 10 when she was diagnosed with secondary combined immune deficiency. Within a year,

her health had deteriorated to the point that her parents were told they could take her home on palliative care, or contact Szabolcs and the pediatric lung transplant team at Children's to explore whether she could enroll in their clinical trial. She was 11 when she was added to the transplant waiting list. She received her new lungs in September 2015; a month later she celebrated her 14th birthday at the Ronald McDonald House in Pittsburgh. Her new bone marrow was transplanted in January 2016. Today, she's applying to college.

"That was a thing I didn't think she would get to do," says her mother. "When she started getting sicker and sicker, there was a part of me that started trying to prepare myself for a life without her. It's amazing that she's here."

Like Daphne, Madeline achieved immunological tolerance. Her mother still urges her to avoid people who are sick and wash her hands often, but Madeline has no need for immunosuppressant therapy to protect her lungs from rejection. Her donor bone marrow takes care of the job, simultaneously fending off the ear infections, pneumonias, and other ailments that plagued her during childhood.

But unlike Daphne, whose native immune system was totally obliterated and replaced in full—a state known as full donor chimerism—some of Madeline's own stem cells survived. As a result, her blood contains mature cells derived both from her own bone marrow and that of her donor's, a state known as mixed chimerism.

Szabolcs and his collaborators don't yet understand why Daphne's immune system exhibits full chimerism while Madeline's is mixed. Both outcomes have long been documented among bone marrow transplant recipients, with mixed results. "Even with full dosing," says Szabolcs, "some patients reject [the bone marrow transplant], some fully engraft, and some live with fully mixed chimerism. It wasn't something people could control; it just happened."

Chimerism first attracted scientific attention in the 1940s—cattle twins sometimes exhibited two distinct immune types, antigens acquired during their mutual gestation. Later, doctors reported similar cases among humans. Evidence of such chimerism in nature suggested that clinicians might be able to induce the state in transplant patients, subverting or short-circuiting the dangerous scenario of donor and host immune systems clashing.

In the early '90s, when Szabolcs was a postdoctoral fellow in New York City, he heard Pitt transplant pioneer Thomas Starzl give a talk on the subject at Rockefeller University. Starzl had started documenting mixed chimerism among liver transplant recipients, some of whom had successfully abandoned their anti-rejection medications. He had a hunch that the key to their immunological tolerance was derived from what he dubbed "passenger leukocytes." That is, white blood cells from donors were hitching a ride on transplanted livers; in the process, they were conferring mixed chimerism to the recipients.

Starzl hypothesized that those donor-derived leukocytes were the key to immunological tolerance. In his subsequent experiments, says Szabolcs, Starzl simply transfused donor bone marrow—recipients didn't receive myeloablative conditioning and the donor cells weren't processed to reduce the risk of undue aggression against the recipient.

"They didn't have the specific objective to engraft stem cells and build the immune system," says Szabolcs. "Our primary point is to transfer the immune system from the donor, and then there's a realistic possibility that tolerance could also develop."

To better understand what's going on with their own patients—both teens and adults, several with significant comorbidities—Szabolcs and McDyer spend a lot of time in their respective labs, analyzing bloodwork and cells washed from their patients' bronchial passages, looking for clues to long-term prognoses. In addition to making sense of how chimerism relates to immunological tolerance, they're also documenting the myriad forms mixed chimerism takes. Already, they know that certain cell types in the bone marrow exhibit asymmetrical host-donor ratios, even in the same patient—but the implications of those differences remain murky. They're also investigating how close matches must be for a successful outcome.

"These are patients who don't have other options," says McDyer. "We tell them it's a lot of risk, and we learn a lot from each patient, and we'll do our best—we'll do everything we can to get them through it." ■