In the spring of 1962, in the suburbs of West Philadelphia, the Shlomchik family prepared for the arrival of their second child.

“Mark,” Marlene said to their toddler, “you’re going to be a big brother. You’re going to have to take care of the baby.”

The Shlomchiks were worried about the new addition to the family, and with good reason. Marlene was B negative, Seymour was O positive; and as a surgical resident (a future orthopaedist), he was well aware of what the antibodies in his pregnant wife’s blood work meant. Her immune system—piqued and primed by the Rh-positive blood that had crossed the placenta into her system when she carried her first child—was now mounting an attack on her second.
The couple arranged to deliver at Einstein Medical Center, the Philly hospital best equipped for what the baby would need—delicate exchange transfusions to remove his own blood and replace it with that of a donor. Given the risks—including brain damage—associated with coming into the world with high bilirubin levels and self-destructing red blood cells, time was of the essence.

Mark, a 26-month-old, took his new charge seriously. On the day his parents came home without the baby—a boy, Warren, who would stay in the hospital for seven exchange transfusions in all—Mark stood at the door, dismayed.

"Where's my brother?"

Fortunately, Warren not only survived, but thrived, turning out just as bright as his brother (which is saying a lot—Mark was giving his classmates astronomy lessons in kindergarten). And since the day Warren came home, "they've been really close brothers and best friends," their father says. "They've never been competitive with each other. They used to play tennis and never kept score."

Mark Shlomchik, an MD/Ph.D.—a specialist in transfusion medicine when he wears his clinical hat and in immunology when he wears his academic hat—arrived at the University of Pittsburgh as the new chair of the Department of Immunology in October 2013. Best known for his discoveries in the essential biology of lupus, he was among the first to elucidate the roles of B cells and of toll-like receptors in autoimmune disease.

Warren Shlomchik—the taller, dark-haired brother who looks a lot like their dad, if their dad wore a ponytail—is an MD who studies the immunology of allogeneic stem cell transplantation, especially situations where the donor's immune cells attack the host's malignant cells or the host's body more generally. A hematologist/oncologist, he's making preparations to join his brother at Pitt in March 2015 as professor of medicine and director of Hematopoietic Stem Cell Transplantation and Cell Therapies for the Division of Hematology/Oncology and scientific director of Hematopoietic Malignancies for the University of Pittsburgh Cancer Institute (UPCI). (When his family joins him, Pittsburgh will inherit one of Connecticut's top dermatologists, Warren's wife, Stephanie Dietz.)

The Shlomchik brothers—to whom we'll refer by first names, for clarity—have a history of sticking together.

Mark went to college at Harvard. Then so did Warren. Mark went to med school at Penn. Then so did Warren. Mark spent much of the past 20 years working in one of the top immunology departments in the country, Yale. And Warren has done that, too.

And for much of that time, they've been scientific collaborators.

"We have a great time with it," says Mark. "We used to see each other practically every day."

"We no longer read each other's grants. But we read sections of each other's grants," says Warren.

Mark's predecessor, Olivera Finn, PhD Distinguished Professor of Immunology and of Surgery, and founding chair of immunology at Pitt, says there's nothing bittersweet about handing over the reins—it's "all sweet." New leadership means new resources and new faces in this department she built from scratch 12 years ago, when she recruited four basic scientists (young scholars fresh out of their postdocs, all of whom went on to make tenure on the first try, she notes). Finn calls Mark a prime choice for the job. In fact, in the '90s, when she was at Duke, she tried to recruit him.

At Yale, Mark and Warren were just down the hall from each other, but in Pittsburgh, Warren will be a few floors away, in the Thomas E. Starzl Transplantation Institute—not because anyone wants to break up the Shlomchik brothers, but because Warren will be close to collaborators there. Immunology at Pitt is expanding. And just as important, it's strengthening its ties to departments and centers across Pitt and UPMC. (Since he arrived, Mark has already been at the table for faculty searches in pediatrics, rheumatology, and oncology.)

These changes reflect a growing appreciation for immunology as central to virtually every part of medicine, from arthritis to transplantation, from asthma to vaccine development, and across a host of immune diseases and disorders affecting every organ system and every phase of life.

When we science scribblers write about immunology, we tend to lean on the same old, tired metaphor—war. And, as with many clichés, this one is popular because often, it fits: Antigen-presenting cells are something akin to intelligence officers, spotting pathogens and sounding alarms. B cells and T cells—the immune system's infantry—deploy and attack. Antibodies—like heat-seeking missiles—search and destroy. And when all goes well, the viruses and bacteria fall, and the body lives another day.

But at a certain point, the good-guys/bad-guys trope falls short—and so do scorch-earth approaches to disease. If you bomb all the body's bacteria into the Stone Age with antibiotics, the microbiome is left in ruins. If you shut down all of an autoimmune-diseased body's defenses with immunosuppressive drugs, then that body is a sitting duck for infection and for cancer. And if you obliterate tumors but wreck the body along the way, then it's all for naught.

As we're getting to know our basic biology better in the quest for more targeted therapies, we're seeing a much more nuanced picture: competing agendas, balancing acts. As one Stanford writer put it, the relationship between microorganisms and the bodies they inhabit is more like a "finicky marriage" than a war. Somehow, everyone must find a way to coexist under one roof—like a family. And a persistent curiosity for these underlying mechanisms has fueled both Shlomchik's studies from the start.

In Mark's first year of med school, his immunology instructor invited him to work in his lab. And within the first few weeks of that summer job, Mark was hooked. So hooked that he decided to take a year off and apply to graduate school. So hooked that, when he was done with his PhD, he wasn't sure that he wanted to go back for his MD, he was having so much fun. By then he'd already racked up five first-author papers that would be published in journals like Nature—early studies on the origins of autoanti-
bodies that are still widely cited.

But go back to med school he did. His dad, among others, convinced him that being an MD/PhD would help him in the field he was so in love with, autoimmune disease research. (“And I was right!” says Seymour.)

When it came time to pick a clinical specialty, the study of blood, and all of the secrets it tells on the immune system at work, appealed to Mark. “Transfusion medicine is immunology in action.”

To date, his longest-running collaborator, actually, is not his brother, but Ann Marshak-Rothstein, PhD professor of medicine at the University of Massachusetts—she's been a “critical” partner, he says. They met at an autoimmunity conference when Mark was a PhD student. Marshak-Rothstein went up to Mark's mentor, Martin Weigert—a “brilliant scientist,” she says, whose lab was among the first in the country that could efficiently sequence antibody genes. Marshak-Rothstein had isolated from autoimmune mice some cell lines that secreted monoclonal antibodies that reacted with the mouse's own immunoglobulins, something that only happens in disease. She thought that sequencing could reveal a lot of the origins of the antibodies. She pitched the idea to Weigert at the meeting, but his plate was full, and he had to turn her down.

“But about 15 minutes later, Mark walked over and said, 'Just send me your cell lines. I'll sequence them,'” she recalls. It turned out to be worth everyone's while—to the tune of a Nature paper (1987).

The monoclonal antibodies, or rheumatoid factors, were the same sort that circulate in the blood of a mouse model of lupus, as well as in people with lupus and rheumatoid arthritis. After completing medical school and residency, Mark worked again with Weigert, this time to create a mouse with B cells only expressing rheumatoid factor receptors. The result was an ideal setting for studying the molecular play-by-play of a self-destructing immune system in the throes of lupus. Thirty years later, Mark and Marshak-Rothstein are still using the model for their studies.

In autoimmune diseases, the body is attacked by various stripes of autoantibodies, which might be thought of as specialized “heat-seeking missiles.” Patients with lupus produce autoantibodies that attack DNA and RNA, we’ve long known, but the reasons why have eluded scientists. Of the hundreds of thousands of proteins and different molecules in the human body, why were DNA and RNA the preferred targets of the self-reactive B cell response in lupus? Although DNA and RNA dwell in cell interiors, they are constantly released from dying cells; many thought the link to cell death was important.

In 2002, Marshak-Rothstein and Mark Shlomchik unraveled this mystery. B cells that bind to immune complexes that contain RNA and DNA get an extra boost because of another class of receptors, called toll-like receptors (TLR), that can recognize either DNA or RNA. TLRs play a critical function by helping the immune system recognize DNA and RNA from bacteria and viruses—scientists used to think they could only recognize these pathogens. However Marshak-Rothstein and Mark discovered that DNA and RNA–specific B cells can use their surface receptors to bring these nucleic acids inside them, where the TLRS reside, to activate the TLRS. Once the B cell surface receptors are activated, the B cell goes turncoat, making antibodies to a patient's (own or “self”) DNA and RNA, eventually leading to lupus.

This was big B cell news. Scientists had always assumed a B cell could only activate this self-destruct mode if signaled to do so by a T cell, but now it was clear that wasn’t the case—the TLR could do the job, provided that the B cell recognized either DNA or RNA. B cells and T cells can either act alone or egg each other on in a vicious cycle, Mark and Marshak-Rothstein believe.

In 1994, in his first paper at Yale, Mark showed that B cells were far more insidious in lupus pathogenesis than anyone had ever imagined. Everyone thought they made DNA-targeting missiles (which turned out to be correct). But Mark showed there was another role that’s probably even more important: B cells recruit T cells to kill host cells outright; these TLR-activated B cells could be the missing link to explain how both B and T cells get activated to cause lupus.

Since his arrival in Pittsburgh, Mark has initiated work on a new project funded by the inaugural Lupus Insight Prize, which he received in June 2013. Scientists had postulated that a factor (an enzyme called NADPH oxidase) could lead to inflammation and perhaps promote lupus. Mark’s lab turned this notion around, revealing that a mouse model of lupus was actually highly protected from lupus by the enzyme.

He then recognized that women who lack the factor in half of their cells (it typically shows up in all of our cells) have a 10–20 times higher risk of getting autoimmune diseases. Subsequently, other labs have shown that having any one of a large series of relatively rare mutations in the gene that codes for the factor also increases the risk of getting lupus by a substantial margin. The $200,000 award will enable him to further probe his lab’s findings in hopes of revealing new therapeutic targets.

Mark’s focus on B cells in lupus has also driven him to investigate normal B cell immune responses, which are required to clear bacteria and viruses and for vaccines to work. Particularly intriguing in this regard are “memory” B cells that have responded to a vaccine, then live on, waiting to protect the vaccinated person if he or she should ever encounter the real virus that is the subject of the vaccine. Mark is now working to define the various subtypes of memory B cells. He also has a new project on B cell activity in infectious diseases, specifically influenza and salmonella.

Mark is well-known for investigations like this—he’ll often create new mouse models that enable him to figure out the roles of various autoimunological minions. Some drugs that can be used for autoimmunity have been inspired by his studies of lupus in mice.

Whether he’s in the lab or out, Mark is known for being almost always in the zone—and that’s a zone where he’s always front and center. "He's the main man," says his brother: "Mark knows a lot about a lot of things. He always has. Going back to reading the encyclopedia when he was growing up."
gery, of immunology, and of medicine, and scientific director of the Thomas E. Starr Transplantation Institute. Both were recruited from Yale, like Mark (in 2009 and 2005, respectively).

At Yale, says Lakkis, Mark functioned very much like immunobiology was his primary appointment. (It was actually secondary; his primary appointment was laboratory medicine.) “He did things,” says Lakkis, “that took a lot of effort to advance everybody’s work in the department.”

Like completely reorganizing a centralized flow cytometry core, notes his brother.

“He’s a doer,” says Rothstein.

Mark led the charge to renovate his department’s space on the 10th floor of Pitt’s Biomedical Science Tower East. (So far half of the floor is finished, and it’s beautiful: an open-plan lab, separate office space, and lots of light throughout. “They actually cut extra window holes into the building,” Mark says.)

Another Pitt example: Mark’s faculty recruitment campaign since coming here. “Everyone nationally has noticed that as Mark was first setting foot here, he was already signing a very, very prominent researcher,” says Rothstein. (That prominent researcher is Dario Vignali, a PhD, Pitt’s new vice-chair of immunology, and UPPI’s coleader of cancer immunology and of its Tumor Microenvironment Center.)

With Mark’s Lupus Insight Prize in hand—

and his lab now up and running in the clinical research powerhouse that is Pitt/UPMC—he’s eager to take the insights he’s gleaned from studies of basic biology in the lab and test them out in the clinic. He finds the prospect exciting, but it’s a new area for him.

“How you do really effective human research and get insight into human diseases is not trivial. It’s very humbling,” he says. “There’s a number of people who do this very effectively at the School of Medicine, so I’m hoping to learn from them.”

On a warm afternoon in August 2014, in the student union of Pitt-Greensburg, which is about 35 miles from Oakland, students trickle in and out of the dining hall past a table with a banner that reads BE THE MATCH—promoting participation in the national bone marrow—donor registry.

Throughout the day, some 34 Greensburg students step up to dab the insides of their cheeks with cotton swabs; their DNA samples will be sent to a central lab in Minneapolis for processing. About one in 100,000 of such registrants matches up with a patient in need of a transplant who has no donor match within the family—as is the case about 70 percent of the time. Typically used in patients with leukemia, lymphoma, or aplastic anemia, this type of transplant is not without significant risk to the recipient; however, it is a chance for the patient to be cured.

“Theres a lot of explaining,” says Grace Huber, a community engagement representative for Be The Match. People commonly call it bone
marrow donation, but more precisely, it’s a donation of hematopoietic stem cells, which come from bone marrow only 25 percent of the time. The rest of the time, the stem cells are harvested from circulating blood. (In this context, “stem cell” means immature blood cells—not embryonic cells.)

The field of stem cell transplantation is specialized, and there’s a lot to explain—even when the person who walks up to her table happens to be an MD, says Huber. “They just don’t know—unless [the person] happens to be a transplant doctor.”

A doctor like Warren Shlomchik.

The same back-to-school week as the donor registry drive in Greensburg, the younger Shlomchik brother talks with this writer via phone, breaking for coffee while on clinical rotation at Yale-New Haven Hospital. He is a professor of medicine and immunobiology at Yale and codirector of the Yale Cancer Center’s program in Cancer Immunology until March 2015, when he moves to Pitt.

Part of the original rationale for stem cell transplantation was to allow patients to receive high doses of chemotherapy/radiation therapy so as to kill leukemia cells that survived less intense treatments. These high dose therapies would, unfortunately, also kill the patient’s normal blood cells. This toxicity could be “rescued” by giving donor blood stem cells (originally harvested from bone marrow) that were free of leukemia cells. However, even the earliest practitioners of this once exotic therapy recognized that immune cells (later revealed to be T lymphocytes or T cells) from the donor could attack patient’s leukemia cells, Warren explains. “This was recognized in mouse experiments done in the late 1950s.”

So with the transplanted cells, the patient receives immunosuppressants—not primarily to keep the body from rejecting the donor cells, as you might expect, since that’s how it usually works when a patient receives a donor organ.

In stem cell transplantation you’re also trying to keep the transplant—the new immune system—from rejecting the body. This deadly complication, also caused by T cells, is known as graft-versus-host disease (GVHD).

Unfortunately, immunosuppressants leave patients vulnerable to infection. Nearly half of all deaths among transplant recipients are largely caused by GVHD and the consequences of immunosuppressive drugs used to prevent and treat it, notes Warren.

Warren followed a somewhat winding career path. As a college sophomore, a biochem major, he worked in a lab that studied gene expression in flies—at least partly for med school applications, at first. Yet Warren found he liked research so much he took a semester off from school to stay in the lab. Developmental biology fascinated him: hormones altering destinies, cell lines reinventing themselves. By then, the undergrad who’d always pictured himself as purely a clinician, like his dad, realized he wanted to do that and be a basic scientist.

Again, blood was a compelling story for a Shlomchik brother; Warren now practices hematology and oncology.

“Forming the different types of blood cells requires differentiation, very akin to what my interests were in college. . . . And likewise, cancer is an example of development that has gone wrong.” He adds that some subliminal influence likely stemmed from his mother, as well—Marlene Shlomchik died of breast cancer his senior year of college.

After Warren graduated from medical school at the University of Pennsylvania, he did an internal medicine residency at Cornell/New York Hospital, then returned to Penn for a hematology/oncology fellowship (after a year as an emergency medicine doctor). His first year into fellowship, he read a paper in The New England Journal of Medicine that changed everything for him.

It was a series of bone marrow–transplant cases. The patients’ leukemia returned even after their transplants—however, the patients were successfully put back into remission after receiving white blood cells from their donors. “I thought that was pretty amazing,” he says. Some of the patients ended up with GVHD, however.

Though at this point Warren had planned to enter a lab that studied blood-cell differentiation, he altered his course. The idea he had at the time was to put a gene in the donor T cells that would allow them to be killed if GVHD developed. Warren learned from Mark that there were mice that expressed a “kill gene” in specific subsets of T cells, and together they began pursuing this approach in mouse models of GVHD in Mark’s lab at Yale and in Stephen Emerson’s lab at Penn. Warren also began working on putting a kill gene into the T cells, though by this time he learned that several other groups were fairly far along on this idea already.

Before working on this mouse model, the only immunology experience Warren had was the single course he’d taken in med school almost a decade prior. He and a close friend at Penn, who also was entering an immunology lab, together began teaching themselves immunology. Fortunately, throughout these self-directed studies, whenever Warren had questions, there was Emerson. And, well, he knew this other guy.

“My brother was very much my mentor,” he says. “He had vast knowledge and experimental approaches and techniques.”

The GVHD model was one of many collaborations to come between the brothers.

Warren’s first big splash in GVHD started as a side project while he was still a postdoc. It had to do with antigen-presenting cells. These APCs, as they are called, take up pathogens, or cells that have been infected, and present them to T cells. In this way, the APC sort of alerts the immune system about undesirables (viruses and the like) in the neighborhood.

That’s how it’s supposed to work, anyway. But in the case of GVHD, stem cell recipients end up appearing to their own immune systems as though they have an infection in every cell.

Warren studied a class of donor cells, called CD8 T cells, that were known to cause GVHD. However, no one could say for sure just whose orders these cells were acting on. Were they getting their intel from the APCs derived from the donor’s cells or from the recipient’s? Warren’s work suggested it was the latter—the hematopoietic-derived host APCs. These unexpected findings ran in Science in 1999.

“I would call it a paradigm shift,” says Pavan Reddy, an MD who is the Moshe Talpaz, MD Professor of Translational Oncology at the University of Michigan. “[Warren] did some really creative experiments. Nowadays everybody does them; but back then, they were quite creative.”

Reddy and Warren are close colleagues, and competitors, in the way you have to be when you’re in such a small field. But the relationship smacks more of sibling than of rivalry. In 2006, Warren helped Reddy reshape a section of a grant application that hadn’t gone over well with the reviewers. The edits ultimately got Reddy his first grant from the National Institutes of Health. (“As it turned out,” Warren says, “Pavan has developed into one of the very top few investigators in our field who is translating his discoveries to the clinic. He certainly no longer needs help from me!”)

Many years ago, Reddy, then a postdoctoral fellow, walked up to Warren at a national meeting and said something to the effect of,
So, you’ve come up with three of the most important ideas in stem cell transplant medicine in the last five years. What other ideas do you have?

Warren laughed and said, Well, I’m not going to tell you!

That “paradigm-shifting” Science paper, of course, tops Reddy’s list of 3. Number 2, which also made ink in Science three years later, was Warren’s collaboration with Italian scientist Andrea Velardi. They showed that natural killer cells—immune cells that had been known to destroy both leukemia cells and antigen presenting cells—could also be deployed to reduce GVHD in both people and mice.

And number 3? That’s become something of an epic feat—a finding first reported 11 years ago that’s finally made it all the way from the bench to the bedside.

The study has to do with T cells. Typically, in a cancer patient, T cells are transplanted with a biotech company called Miltenyi to develop a way to get rid of the naïve T cells, leaving behind only memory T cells. The goal was to administer these memory cells along with stem cells during transplantation, sans naïve T cells. With funds from the Clinical Scientist Award in Translational Research, which Warren received from the Burroughs Welcome Fund in 2007, and an NCI project award granted to researchers at the Hutcheson by Stanley Rickert, an MD, the team is wrapping up a pilot trial of about 48 patients. Warren stresses that the Hutcheson team has done much of the work, notably MD/PhD Marie Blelley: “She has been amazing.”

The results so far are promising, Warren reports. The group will begin a larger-scale, NIH-funded clinical trial in Seattle and Pittsburgh in 2015.

Reddy is psyched about the possibilities, should this approach pan out: “You don’t have from donors along with the donor’s stem cells. The T cells promote engraftment, aid in reconstituting the immune system, and kill cancer cells. Unfortunately, they also cause GVHD.

When Warren first moved to Yale in 2000, he wondered whether different types of T cells behaved differently in GVHD. Would memory T cells—which develop from T cells that respond to infections and then stick around to protect you forever—respond differently from naïve T cells, which had never encountered infections of any kind before?

Working with their mouse model of GVHD, Warren and Mark discovered that memory T cells caused less GVHD but could transfer immunity from the donor to the host. The brothers published their findings in The Journal of Clinical Investigation in 2003. In subsequent work Warren showed that donor memory T cells could also mediate the graft-versus-leukemia effect (in which donor cells recognize leukemia cells and destroy them) and could transfer immunity to viruses from the donor to the host.

Warren and his collaborators at the Fred Hutchinson Cancer Research Center in Seattle (a.k.a., “the Hutch”), funded by a grant to Warren from the NIH Rapid Access to Intervention Development program, worked to tinker with cells, you don’t have to add a new drug. . . . You could get all the benefits without the downsides.”

Immunosuppressants are a cruel irony in solid organ transplantation, too. The very medication that keeps the body from rejecting its life-saving organ can also open the door to both infection and cancer. Because stem cell transplantation is a rebirth of the immune system—really, a sort of resowing of the donor’s immune system in the recipient’s body—Starr Institute investigators have been following Warren’s work with interest. “If you’re able to [safely] give a bone marrow transplant,” says Pitt’s Lakiss, “then you can turn around and transplant organs from that same donor without having to give any immunosuppressant.”

“This is the most promising strategy for tolerance.”

Lakkis and Rothstein have been collaborating with Warren since 2001—and have been lobbying to bring him to Pitt for years. Working together has been illuminating for all involved, as their fields face many of the same questions—because organ rejection and GVHD are mirror images of each other. Remember, in the former, the body rejects and attacks the organ. In the latter, the new cells reject the body.

The Yale/Pitt team has studied both processes at their most fundamental levels, using a powerful imaging tool called intravital two-photon microscopy—a window into the cellular doings within the living animal in real time.

Another reason Rothstein and Lakkis are counting down to Warren’s arrival is the opportunity to witness the signature Shlomchik Brothers Brainstorm again. They’re famous for this: Dispassionately scrutinizing every bit of the data, and then stepping back and seeing the big picture. Spotting the holes in the logic and then laying it all out, no hemming and hawing. Just: Here is the killer experiment you need to do to nail down the story.

Says Lakiss, “They’d come into your lab meeting, listen to your fellows’ presentations, and say, ‘Oh, why are you doing that experiment? Why not do this instead?’ They will tell you that. And it will completely transform your work. But at the same time they’ve become good friends with people. . . . Very generous with mice, reagents, with ideas. There’s no scheming. Just critical thinking.”

And then, says Rothstein, they’ll check up on you: “When you go back to either of them months later, they remember exactly where you left off. It’s like, Okay, did you do that experiment? They’re both very much that way, just very, very bright.”

“Pitt was pretty lucky to get both of them,” says Reddy. “[In] the immunology world and the transplantation world, they’re clearly superstars.”

When Mark won the Lupus Insight Prize, his father flew up from Florida for the big event and took everyone out to dinner.

That night, and the night Mark won a clinical award from the Lupus Foundation 10 years earlier, Mark went up to the mic to receive his prize, and said, “This would not have been possible without the support of my father.” Warren says he feels the same way about what he’s been able to accomplish.

It’s another classic move in this family—the Shlomchik credit-share. Toasting your progenitors. Paying it forward to your brethren. And to the new blood.