THE DOCTOR IS IN

Surgeon Shaf Keshavjee is on a mission that has taken him everywhere from the lab to the operating room to a spot on *The Colbert Report*.

By Darren Gluckman

The incessant buzzing of a surgeon's phone can signal a medical emergency. But when Shaf Keshavjee's phone went haywire one recent weeknight, he wasn't being summoned to the operating room: He was being urged to turn on his TV. The device he'd created, the XVIVO Lung Perfusion System, was debuting on an episode of *Grey's Anatomy*. The system (which has also been featured on television's *House* and *The Colbert Report*) allows donor lungs to be kept alive and oxygenated outside the body (hence the ex vivo nomenclature) for hours at a time, in order to be treated or repaired before being transplanted into a recipient. And by extending the shelf life of lungs in that intermediate stage between bodies, it also increases the overall pool of lungs available for transplantation.

PHOTO BY CARLOS OSORIO/GETSTOCK

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"It was great publicity," says Keshavjee, the surgeon-in-chief at University Health Network, a professor of thoracic surgery at the University of Toronto, and the director of the Toronto Lung Transplant Program. Mild-mannered and friendly, he doesn't conform to the stereotype of the surgical personality, though his office is so clean and sparse that one might suppose it could double as an operating theater. Or that he'd moved in the day before. In fact, Keshavjee's been a fixture at the hospital since his days as a wide-eyed resident, scrubbing in for suture work on the world's first successful double-lung transplant operation. And it's his staying power and his vision that has restored Toronto General's reputation as a world leader in the field of thoracic surgery generally, and lung transplantation in particular (it might be apt to say he's breathed new life into the program).

Not that he hasn't been enticed to go elsewhere. "I've had job offers from many major centers in the States," he says. So what kept him here?

The lung was the last of the major organs to be successfully transplanted. "The problem with the lung," explains Keshavjee, "is it's a very fragile organ. It feels like a soft sponge. It has very thin walls for gas exchange and has a unique anatomy in that it has two blood supplies: There's one to pick up oxygen and drop off carbon dioxide, and then there's the nutritive blood supply called the bronchial circulation. When you do a lung transplant, you don't completely hook up the bronchial supply. So the Achilles' heel of the operation was that you could transplant the lung, but then 10 days later, the airways would fall apart and the patient would die. That was the problem that Joel solved."

Joel is Dr. Joel Cooper, who led a team to perform the world's first single lung transplant in Toronto in 1983, and the first double lung transplant—the one the young Keshavjee scrubbed in on—in 1986, also in Toronto. How did Toronto earn this distinction? Through much of the 1980s, Toronto General was the place to be for thoracic surgery. The program was pioneered by Dr. F. Griffith "Griff" Pearson, who Keshavjee describes as "a phenomenal, innovative thinker. Everybody knew that in Toronto, there's this guy, Pearson, and if you want to be a thoracic surgeon, that's where you go. So then Cooper came to train here from Mass General. As did Bob Ginsberg, another giant."

Keshavjee, who'd known since his childhood in Kenya (he came to Canada at age 12; he's now 50) that he wanted to be a surgeon but hadn't settled on a specialty, was interning at Toronto General when he was assigned to the thoracic surgery department. "At the time, I didn't even know what thoracic surgery was," he says. Incidentally, this commonplace ignorance of the term is something that he wants to correct. Everyone knows what *cardiology* means. Or what a neurologist looks at. *Thoracic*—having to do with the organs of the chest, the lungs and esophagus (and, yes, that bloody heart)—sends most people to their dictionaries (or, let's face it, to Google).

But once Keshavjee had familiarized himself with the terminology and the terrain, and had met Pearson, Cooper, Ginsberg, and Alec Patterson, among others, "I realized that these were the greatest thoracic surgeons in the world. Thoracic surgery began right here, at Toronto General, and I was right in the middle of it with these guys."

Ginsberg's calm brilliance was a factor in Keshavjee's decision to become a thoracic surgeon. He remembers the very day it happened. He was in the operating room, watching a junior surgeon assess a malignant lung tumor. The surgeon noted that the tumor was growing into the heart and concluded that the cancer was therefore inoperable. At that point, Ginsberg entered the theater, examined the problem, and nonchalantly declared that they could simply lop off that part of the heart as well. Which is what they did. The operation was a success, and Keshavjee never looked back. The high-wire aspect of the profession is part of its appeal. He cites "the intensity and speed of thinking. You don't sit around for three or four days, mulling it over. You don't have that kind of time." (An amazing testament to the power of the will over cognition is the fact that Ginsberg—a lung cancer surgeon all too familiar with the risks—smoked a pack of cigarettes a day and would die of lung cancer, in 2003, at the age of 61.)

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Accepted into the surgeon-scientist program at the University of Toronto, he was offered the chance to work in the lung transplant program with Cooper. "I said *the* Joel Cooper?" he recalls. Prior to 1983, lung transplantation had been tried over 40 times without success. Cooper's envelope-pushing persistence, his conviction that it could be done, provided a model that Keshavjee would later emulate in his own practice. In the meantime, he knuckled down and completed the decade-long training process to qualify for the job. But a funny thing happened on the way to the operating room: The department disappeared.

"I stand on great shoulders," he acknowledges, "but as much as I respect those guys, they had no succession plan. We had the best thoracic surgeons in the world here, but between 1988 and 1994, they all left. Ginsberg went to Sloan-Kettering, Cooper and Patterson went to St. Louis, Mel Goldberg went to Philadelphia, Paul Waters to UCLA. The best in the world disappeared. Toronto General was looking like a shell of itself for thoracic surgery. We were left with Canadians going to Harvard to be operated on by a Toronto-trained surgeon. And that bothered me."

So he stayed and, with the management skills to accompany his medical expertise (he's no gastroenterologist, but cites Jack Welch's *Straight From the Gut* as an influence), he rebuilt the department. He established the Pearson-Ginsberg Chair in Thoracic Surgery. He was able to recruit Dr. Kazuhiro Yasufuku from Japan to lead the field in developing minimally invasive and ultra-minimally invasive thoracic surgery techniques, luring him with a new $7 million facility where Yasufuku is finding ways to detect lung cancers when they are no larger than three or four cells, and creating tools to do lung surgery through a bronchoscope so that external incisions aren't required. The division, which is now averaging a lung transplant almost every other day ("I did one this morning"), did a robotic lobectomy last week. "My gut feeling," says Keshavjee, "is that using robotics to enhance our human capabilities will be the future of better, more precise, more effective surgery. The robots we have now are probably clunky Model Ts. But you've got to start somewhere. And we need to be in the front line with that." And Keshavjee, no slouch as an innovator himself, has made his own contributions to the field, which have not only found their way onto prime-time television, but into the domestic doyenne Martha Stewart's Twitter feed (to which we'll return).

The result of these efforts, he notes, is that Toronto-trained surgeons now head every major thoracic unit in North America (including three of the six staffers at the Mayo Clinic). And, at home, "we've got the best thoracic surgeons again, where every member of the division is in the top one or two percent in the world," he boasts. "We have exceeded the height of that fantastic division that I was looking at as a student."

How did he turn things around? "I told the story," he says simply, citing the Menkes family and Albert Latner as key philanthropic supporters. "What made Harvard great, what made Stanford great, is that people cared enough about those institutions [to invest in them]. People need to know what we're doing because they want to back a winning team. If you go anywhere in the world and say, 'I'm a thoracic surgeon from Toronto General Hospital,' you're immediately recognized as an elite brand, the top of the pile." He sighs. "But the average Canadian walking in the door doesn't know that." Nor does the average Canadian philanthropist or, for that matter, the average Canadian politician. Support from each constituency is critical.

A year ago, in order to address this gap in public awareness, he engaged the services of Level5, a brand development company, to reevaluate the division's Web presence, its messaging, its core DNA, and whether to lose the term *thoracic*, to replace it with something a little simpler or sexier, something that might compete with *cardiologic* in terms of household recognition. In the end, they decided to keep it and branded the concept DOTS, Doctors of Thoracic Surgery. What's next? Keshavjee is *not* asked whether there was any consideration of borrowing some of that Spielbergian magic and renaming the division Thoracic Park. He *is*, however, asked something equally ridiculous.

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For his master's thesis, Keshavjee developed a technique to preserve donor lungs that has increased the number and success rates of transplant operations. "At that time, the way we preserved the lungs was really primitive. We basically collapsed the lung and cooled it down." Preservation solutions are generally designed to slow down the metabolic function of an organ and thus delay the rate of its demise. "It seems obvious now," he says, but Keshavjee recognized that the lung, unlike other organs, is full of oxygen. So that while it has no blood flow, its aerobic metabolism can be maintained.

He decided to take advantage of this; instead of paralyzing the lung cells with potassium and other ingredients, his solution (in both senses of the word) would feed them oxygen and glucose. "We realized," he explains, "that by better preserving the lung, you could improve retrograde blood flow from the pulmonary arterial circulation to the bronchial circulation to keep the airway alive." Don't hold your breath for an explanation of this explanation. It is enough to know that as a result of Keshavjee's solution, which is now commercially produced as Perfadex and is in worldwide use, whereas the first lung transplant recipients were given 50-50 odds of making it through the operation, today's figure is closer to 95 percent. But Keshavjee wasn't done.

Having figured out how to better preserve lungs, he then showed that they could be genetically modified—while still in the donor—to prepare them for the stresses of transplantation, reduce the severity of the recipient's immunological attack on them, and increase their post-transplant functionality. "But it's a bit cumbersome," he says, leading up to his latest showpiece. "We have to fly all over the country, go to another hospital where someone is brain dead, put the vector in the lungs, wait for 12 hours for the lungs to take the vector up, and then take them out for transplant. So I said I want to be able to take the organs and treat them outside the body. But the way we preserved lungs was to cool them down. Once you cool them down, you shut them off, and once you shut them off, the incorporation of genes, gene expression, metabolic functions—nothing works. So how can we keep them at normal temperature?"

The answer is his mechanical baby, his TV star, the XVIVO system, which allows physicians to assess the organ, diagnose it, fix what needs fixing, confirm the fix has been effective, and then "transplant a known, predictable product with a more predictable outcome." Fifty-four lung transplants have been done in Toronto with this system. "They've done about 10 in Madrid," he says, "some in Vienna and England, and, through an FDA trial, they've just done four in the United States, so they're starting to take off everywhere. We're developing a liver one, too. This will apply to all organs. It's going to be an organ repair center. Personalized medicine for the organ. Diagnose what's wrong with it, optimize it, make the organ whatever you need. Use your stem cells to make that organ look like you so you won't fight it for the rest of your life."

Currently, lungs are treated in the XVIVO system within four to six hours, and sometimes up to 12 hours. But Keshavjee wants to extend this window, perhaps for as long as three days. "Where we're going with this is this system will be a bioreactor to grow new lungs. We're working on projects where we take a lung that's damaged, strip it of all its cells, and use the leftover structure as a scaffold, if you will, to put your own cells in and make a lung that looks like you. So if you have lung disease, we'll take your bone marrow stem cells, make lung cells, and create a lung that's yours, and put it into you." If it sounds Frankensteinian, Keshavjee insists it's doable. "Right now, we're doing gene repair or gene modification of a lung that needs to be transplanted. The next step will be cell repair. The next step will be to grow a new organ. The challenge with

regenerative medicine is, how do you change a heap of stem cells into a complex organ like a lung or a heart? An intermediate step is to reline the vascular side, the blood vessel side, with blood vessel cells derived from your bone marrow, reline the airway side with airway cells, and create a lung. It's not that far away. Yes, it's a big step, but it's been done in rat lungs."

He demonstrated the XVIVO system at the 2010 TEDMED conference in San Diego (the video's on YouTube), wowing attendees with a healthy pink pair of pig lungs, harvested earlier that day, inhaling and exhaling, expanding and collapsing, with unhurried regularity, just as they'd done in their former host. Keshavjee invited a few audience members up onstage to feel—and to squeeze—the organs. Among the lucky designees was Martha. "It's a good thing," Stewart tweeted, then promptly posted a picture of the moment for the Twitter-verse.

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A fan of high-performance machines, it's no accident that Keshavjee created the device. He admits to driving a Porsche Panamera (and having pushed its limits on the track at Mosport), "but the point of it," he says, "is that I marvel at the technology, at the detail and the precision of an instrument like that." The difference is, the technology that he's developed doesn't simply thrill. And rather than risk lives, it saves them. The remarkable increase in the viability of lung transplantation has meant, for example, that transplantation is now the leading treatment modality for cystic fibrosis. Bucking convention, the Toronto team did the first lung transplant for cystic fibrosis and, as he puts it, "pulled it off."

"These were the highest-risk lung transplants in the early days. There were many reasons not to do them: They're infected lungs, and then you're going to immunosuppress the patient, which puts them at a very high risk for further infection, and they've got multiresistant infections because they've been treated with antibiotics for decades before they come for transplantation. But we said we're going to do them. And today, lung transplantation for cystic fibrosis patients has the best outlook, the best outcome, the longest survival of lung transplantation. There's a group where we could have easily shied away. Instead, we pushed forward and we've led the world. We now have patients alive over 20 years since transplant." In Keshavjee's opinion, "no one should die of cystic fibrosis without being assessed for lung transplantation."

It's not all boundary-busting bravado. The decision to proceed with a transplant is often fraught with difficulty. "If I do the operation and fail, I've shortened your life. And if I don't do the operation, I've failed you in a different way, but I haven't shortened your life." And as he points out, with transplantation, as opposed to, say, surgery to remove a cancer, failure doesn't impact only that patient. A failed transplant means that the donor lungs have been "wasted" when they could have gone to a lower-risk patient.

Okay, a single lung transplant's been done. You were there for the first double. Are you tempted to go for a triple? Keshavjee chuckles. "No, but we are doing other unique things. We've developed surgical techniques where whatever lung size we've got, we can make it fit." This is especially germane for infants, or "neonates" in Keshavjee's parlance. "Also, Dr. Lori West at SickKids developed a technique for transplanting hearts across the blood-type barrier, and we've adopted that technique for lungs. The goal now—more than a triple—is to create a lung that's going to outlive the recipient." And administratively, his goal is to bring all aspects of University Health Network's Toronto General's thoracic practice under one roof. "We have the pedigree, the breadth and depth, and the track record. We've set up different parts: lung transplant, lung cancer, emphysema surgery, pulmonary hypertension, pulmonary rehab, an asthma center, big research trials in interstitial lung diseases, and sleep medicine. So if you've got a lung problem, we're the place. But we're kind of scattered, with these silos that really need to be pulled together in a comprehensive synergistic program to attract and keep the brightest and best in the world working together."

Meanwhile, easing Keshavjee's burden is his 14-year-old daughter, Sara (his wife, Dr. Donna McRitchie, is also a surgeon and the head of critical care at North York General), who programs his iPod; her musical selections fill the operating theater. Miley Cyrus has accompanied some of the most complex surgical procedures ever performed. "But I draw the line at Justin Bieber," says Keshavjee, exhibiting the uncompromising determination of a surgeon spying a mass of unsightly cells. "He gets deleted." LM