Breathing new life into lung transplants

Significant progress has been made in the art and science of transplanting one person’s organ into another’s body in the last decade. But despite all this progress, lung transplants still pose incredible challenges—and they lag behind other types of solid organ transplants in their ability to save patients’ lives over the long term.

Why is lung transplant so tricky, so risky, and so prone to failure? And, more importantly, how can medical science improve the chances of success?

These questions form the crux of a broad range of research in the U-M Division of Pulmonary & Critical Care Medicine, from basic science laboratory studies to clinical trials. In 2007, the division’s faculty and their colleagues published a number of important papers, while continuing to make improvements in the way patients receive care before, during, and after transplantation.

All of this cemented U-M’s position as one of the nation’s premier lung transplant centers—a distinction that was confirmed this past year by the United Network for Organ Sharing during a review of the Lung Transplant Program, and by the Blue Cross Blue Shield Association, which has named U-M one of only 16 Blue Distinction Centers for lung transplants in the nation. The number of patients turning to U-M for pre-and post-transplant care increases every year.

Kevin M. Chan, MD (right), who is the co-director of the U-M Lung Transplant Program, attributes Michigan’s successful program to its multidisciplinary nature, with close cooperation among pulmonologists, thoracic surgeons, pathologists, radiologists, laboratory researchers, nurses, and transplant coordinators.

In the last two years cooperation has increased, as basic science and clinical researchers work together to find answers to the most pressing questions about lung transplantation and how to improve its success.

One such question is why so many lung transplant recipients develop a condition called Bronchiolitis Obliterans Syndrome (BOS). This condition results in a slow, steady increase in scar tissue within the lung, and leads to a decline in lung function that eventually causes failure of the transplanted lung and death. It occurs in up to 60 percent of lung transplant recipients by five years after surgery and is the primary cause of transplant failure in this population.
Below: Mesenchymal stem cells isolated from lavage of lung transplant recipients are donor in origin. Genotype (male vs. female) of mesenchymal stem cells isolated from sex-mismatched recipients was studied by fluorescent in-situ hybridization using X and Y DNA probes.

A-B: The male sex chromosome status of mesenchymal cells obtained from BAL of a male donor lung transplanted into a female host. Red signal indicates X chromosome, and green signal indicates Y chromosome.
A. Cells were scored in interphase. B. A cell in metaphase demonstrating specificity of the DNA probes is shown on the right.

C-D: Demonstrate the female sex chromosome status of mesenchymal cells obtained from BAL of a female donor lung transplanted into a male recipient. C. Interphase cells. D. Representative cell in metaphase.

Unfortunately, this disease—which robs lung transplant recipients of their last hope of survival—is poorly understood. Urgent questions in need of answers include how BOS develops at the cellular level and how it impacts patients at a functional level.

“The only way to answer these questions is by bridging the distance between bedside and bench—that is combining the strengths of our clinical and basic science research,” says Vibha Lama, MBBS, MS (left), a U-M transplant pulmonologist and translational researcher.

A unique translational research program at University of Michigan has led to important discoveries and publications this year in the field of lung transplantation.

In a study published this year in The Journal of Clinical Investigation, a team of faculty led by Dr. Lama reported a breakthrough in understanding the role of local graft-derived cells in solid organ transplantations. Using samples taken from 76 patients who received lung transplants at U-M, they were able to identify for the first time the presence of a progenitor cell, called mesenchymal stem cells or MSCs, in transplanted human lungs.

One of the key features of the team’s work was the demonstration that these MSCs are derived from the donor and not the recipient. This was achieved by determining whether MSCs from patients who had received the lung of a person of the opposite sex were male or female. “We were able to isolate the cells derived from the donor as far as 11.5 years after transplantation, a finding which was both surprising and exciting,” says Lama.
In addition to Dr. Lama, authors of the study were Linda Badri, Hui Liao, Galen B. Toews, MD, Marc Peters-Golden, MD, David J. Pinsky, MD, Fernando J. Martinez, MD, and Victor Thannickal, MD.

Now, the research team is trying to figure out the precise location of the MSC “hideout” in the lungs, and the precise mechanism by which they might contribute to—or perhaps prevent—BOS. Dr. Lama says the patients who allowed their cells to be used in the study are excited by the findings, and by the idea that they are helping find answers to questions that affect nearly all transplant recipients.

Even as U-M researchers work to understand the role of MSCs in bronchiolitis obliterans syndrome, they’re also documenting the impact of BOS on patients and trying to see who is most affected by it. This year, they published findings in the American Journal of Respiratory and Critical Care Medicine.

In this study, lead author Dr. Lama and the research team analyzed lung function patterns in 111 lung transplant patients with BOS, and showed that patients can experience different courses of decline after the onset of BOS. Further, they identified several factors that can predict the course of lung function after BOS onset, a finding which has important practical implications for management of patients with this disease.

The U-M lung transplant program is at the forefront of research and clinical care, and received additional accolades this year from a paper that reviews the success of the U-M program’s first 344 lung transplants, in 339 patients who received transplants between the start of the program in 1990 and September of 2005. U-M patients had better survival rates than the national average—with 79 percent alive at one year, 60 percent alive at three years and 52 percent alive at five years.

The paper, published in the Journal of Thoracic and Cardiovascular Surgery by a team led by Dr. Chan and his colleague Andrew Chang, MD, of Thoracic Surgery, also showed that even though the U-M team has increased the time window for transplanting donated lungs, survival hasn’t suffered.

By extending the amount of time that lungs can be viable after a donor’s death, the U-M team is allowing more organs to be used. But still, the number of lungs recovered from donors is far lower than the number of people who need a lung transplant, so Chan and others are working to help hospitals increase the proportion of eligible lungs that they make available to the transplant network.

The U-M team is working to make the best of every transplant, by offering patients access to the latest clinical trials of anti-rejection drug regimens and infection-prevention medication, including ganciclovir to guard against cytomegalovirus infection. They’re also trying to identify those patients who might be able to avoid a transplant, by getting early, aggressive treatment for progressive lung diseases such as emphysema and pulmonary fibrosis. Further research on patient outcomes may also help steer the transplant-listing process, by showing which characteristics make a person more likely to do well once they receive a lung or lungs.

As they continue toward their goal of making lung transplants less risky and more likely to succeed, the U-M team is continuing to develop funding opportunities for even more laboratory research, and for more outcomes research that can optimize the transplant experience. These two paths to discovery, combined with a strong clinical program, will surely lead to better treatment for patients today and in the future.