Warming up to lung transplants

By Kai-Jye Lou, Staff Writer

Because of structural and inflammatory damage incurred by lungs before and during death, only about 20% of lungs from organ donors are actually useable for transplant.¹ A group at the **University of Toronto** thinks it could potentially triple this figure by treating the organ *ex vivo* with a gene therapy that introduces an anti-inflammatory cytokine—IL-10.

The team has proof of concept in injured human donor lungs showing that the technique repaired existing damage and improved function.²

Injured lungs typically show inflammation and disruption of the blood alveolar barrier, which leads to impaired gas exchange—a measure of lung function. In addition, higher levels of inflammatory cytokines have been linked to a greater risk of transplant-associated complications in donor lung recipients.^{3,4}

“The issue here is that there is a low availability of lungs that are viable for transplant,” said Greg Snell, medical head of the Lung Transplant Service at **The Alfred Hospital**. “Secondly, in patients that receive the transplant, better measures are needed to prevent chronic rejection and prolong the life of the transplant.”

“Many groups around the world have shown that apparently ‘good’ lungs from standard brain stem–dead donors are already damaged at the time of transplant by the inflammatory upregulation consequent of brain death itself,” said John Dark, a professor of cardiothoracic surgery at **Newcastle University**. “There is a good correlation between the levels of proinflammatory cytokines and early complications. In addition, there is increasing evidence that these early events are also predictors for later failure of the graft.”

Earlier studies from the Toronto group showed that IL-10 gene therapy improved lung transplant outcomes in rats and pigs.^{5–7} But the approach could not be applied to human lungs because the chilling technique used to preserve donor organs by slowing metabolic processes also blocks the production of gene therapy products.

The key technology enabling the translation of the gene therapy approach to human lungs came last year when Shaf Keshavjee and collaborators at **Vitrolife AB** developed the Toronto XVIVO lung perfusion system.⁸ The system preserves lungs at normal body temperature, thus maintaining the organ’s metabolic function at a level that allows for the production of significant amounts of IL-10 prior to transplant.

“We are working to answer the question of whether we can modify

lungs *ex vivo* to improve their condition,” said Keshavjee, director of the thoracic surgery research laboratory and the Toronto lung transplant program at the **University Health Network** and the University of Toronto. “Our previous work has shown that we could do this in animals.”

In the new study, Keshavjee’s team connected human lungs deemed unsuitable for transplant to the XVIVO perfusion system. In these lungs, IL-10 gene therapy reduced the production of inflammatory cytokines and improved lung function compared with vehicle.

Tissue samples from treated lungs also had greater expression of tight junction protein 1 (ZO-1; TJP1) than samples from control lungs. ZO-1 forms tight junctions at the blood alveolar barrier that maintain efficient gas exchange.

“We took injured human donor lungs and used gene therapy to repair them to a state that could make them acceptable for transplant,” Keshavjee told *SciBX*. “This method could make more donor lungs available for transplant—potentially two or three times more.”

The results were published in *Science Translational Medicine*.

This is the first described use of IL-10 gene therapy in the human lung that shows a positive effect on measures of function, said Dark. “I hope that lungs undergoing this sort of treatment will be available in larger numbers, will have better early function and better long-term function.”

Snell thinks pretransplant modifications like the gene therapy approach described in the paper “could make available organs that previously would not have been used for transplant and also could prolong the life of the transplant. If you have a good supply of organs, then it may become more viable for patients to receive a second transplant in case the first one fails.”

Dark did say the *ex vivo* perfusion technique is complex and that not many sites around the globe have the dual expertise needed to apply it in conjunction with gene therapy.

The safety of the adenovirus approach also will need additional evaluation. “Clinicians will want to see that the technique does not cause negative effects on the graft itself,” said Snell.

Dark worried that the increased production of IL-10 in the lung may lead to a general immunosuppressive effect that could reduce resistance to infection when combined with the standard cocktail of post-transplant medications.

Keshavjee said the *ex vivo* approach limits the delivery of the IL-10 gene to the lungs. He thinks the localized production of IL-10 should mitigate the extent of systemic immunosuppression caused by the cytokine.

Next steps

Keshavjee said his group is now evaluating long-term outcomes of treated lungs in pigs. These measures include survival, rejection rates and lung function, and whether the approach improves the body’s tolerance to the organ over time.

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—Shaf Keshavjee,
University of Toronto

Snell said the *ex vivo* gene therapy approach could rapidly enter clinical testing as there is a significant population of patients who need a lung transplant but instead are on supportive care.

“These patients would definitely sign on for such therapies,” he said. “Patients in need of a lung transplant may only have seven days to live when placed on supportive care.”

Keshavjee and Snell think the approach could apply to other organs—including kidney, heart and liver—and for purposes beyond organ repair.

“This approach could conceivably be applied to other organs and with other factors that could improve organ function and prevent rejection,” said Snell. “The applications of the current work are not limited to the area of lung transplantation.”

The University Health Network has filed multiple patent applications covering the *ex vivo* gene therapy approach and biomarkers for predicting lung transplant viability. The work is available for licensing.

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