

Dr Liu and his lab members (left, Dr Jenn Lei Jing, a research fellow from China and Dr Junichi Sugihara, a post-doctoral fellow)

Breathing new life into lung research

Dr Mingyao Liu, from the University of Toronto's Department of Surgery and Institute of Medical Science, has devoted his career to the study of lung disease and the challenges involved in lung transplantation. Uncovering the cellular and molecular mechanisms underlying acute lung injury, he is now at the cutting edge of developing new targets and delivery systems for therapeutics.

As Head of the Respiratory and Critical Care Research Group at Toronto General Hospital Research Institute, University Health Network, Dr Liu is ideally placed to progress research from the bench to the bedside. In a glittering career spanning China, the US and Canada, Dr Liu has teamed up with his colleague Dr Shaf Keshavjee to develop ambitious research goals. These goals have the ultimate aim of overcoming key obstacles in lung transplantation and improving outcomes for patients.

A NEW CANADIAN PIPELINE

Inflammation and cell death are the two key complications following lung transplantation; blocking them to prevent lung injury significantly impacts success rates and patient quality of life. A major focus of Dr Liu's work is therefore on developing methods to protect and repair the donor lung, increasing its tolerance for the transplantation process.

THE PERFUSION PARADOX

Transplantation is a traumatic event for lung tissue, which may be deprived of

blood for significant periods during the process (ischemia). Paradoxically, the return of the blood supply is most damaging to the cells through a process known as reperfusion injury. As the blood flows into the newly transplanted tissue, an imbalance of signalling molecules and the sudden flood of oxygen results in an increase in inflammation and cell damage. White blood cells carried in the blood then release their own inflammatory mediators, contributing to the destruction.

One way of mitigating these effects is to reduce the temperature of the tissue to slow its metabolic rate – a solution not without its own complications. To deal with this set of challenges to lung tissue, Dr Liu and his team have developed a novel cell culture model, where potential treatments can be evaluated *in vitro* (literally 'in glass', to signify laboratory-based studies as opposed to those in living organisms). This gives researchers the opportunity to investigate which factors are in play during this rush of inflammatory signalling, helping them to identify how they could be suppressed.

Inflammation and cell death are the two key underlying mechanisms of acute lung injury following lung transplantation; blocking them to prevent lung injury significantly improves patient quality of life

GOLD-STANDARD RESEARCH

Coupling this with a novel drug delivery system, which harnesses gold nanoparticles to deliver short peptides as specific therapeutics to the target cells, the team are squaring the circle of acute lung injury, bringing molecular therapies to bear on the identified cellular mechanisms. Another method they have pioneered is self-assembling peptide complexes – engineered peptides which aggregate together in a specific formation, enabling hydrophobic compounds (insoluble in water) dissolved in water to access the cytoplasm (interior matrix) of target cells through endocytosis (drawing in of external proteins by the cell membrane).

Dr Liu initially uncovered the pro-inflammatory activity of artificial lung ventilation, which is vital in transplant surgery, through his discovery of the 'mechanosensing' (reaction to mechanical stress) mechanisms which mediate this phenomenon. His early work on pulmonary surfactants in China (designated by the World Health Organization as essential medicines for healthcare systems) was followed up with this pioneering work in the US and Canada, identifying the key inflammatory molecules involved.

KEEPING HOPE ALIVE

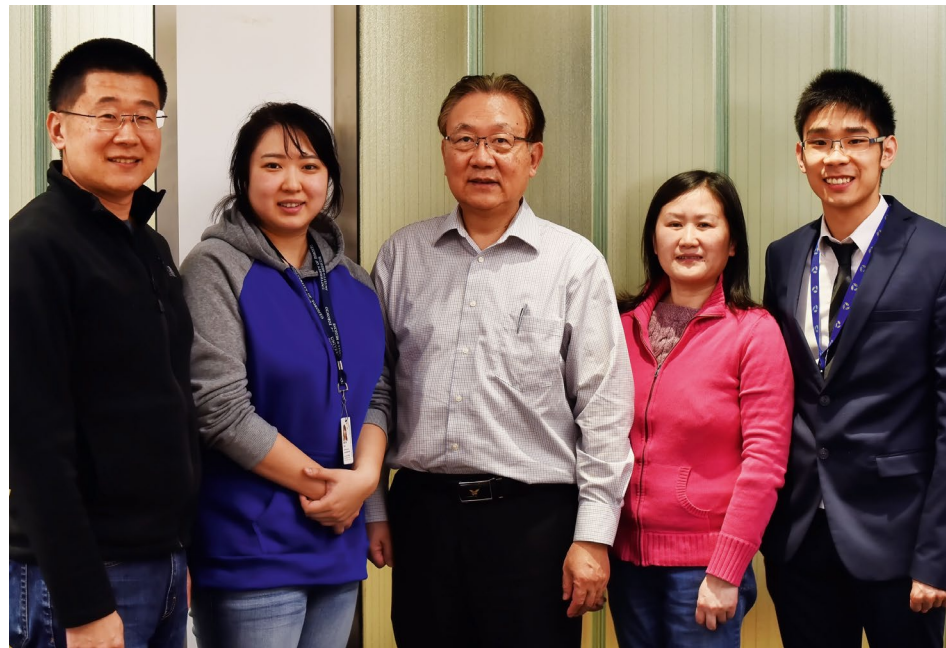
Dr Liu and Dr Keshavjee have been instrumental in developing the Toronto *Ex vivo* Lung Perfusion System (EVLP) – a technique for maintaining, treating and assessing donated lungs for transplant. Using bespoke equipment and perfusion fluids containing selected nutrients and drugs, EVLP makes it possible to artificially maintain a breathing lung outside of the body. This gives clinicians valuable time to test and assess the full physiological function of the donated organ, and establish whether it is suitable for transplant. As such, the use of EVLP technology ultimately improves patient outcomes.

EVLP remains one of the most important recent breakthroughs in lung transplantation. Dr Liu continues to be involved in uncovering specific signalling processes which contribute to inflammation during reperfusion. Just as important are his efforts to develop bioinformatics approaches (methods to analyse biological data) to assess the suitability of lungs for transplant. Dr Liu is looking at cell type-specific biomarkers in lung transplantation, and specific therapeutic targets through genome wide research.



Dr Liu with his post-doctoral fellow, Dr Junichi Sugihara (front), and Scientific Associate, Dr Yingchun Wang (back)

Dr Liu alongside some of his lab members, from left to right: Dr Junichi Sugihara (Post-doctoral Fellow), Hae-ra Cho (PhD candidate), Dr Yingchun Wang (Scientific Associate) and Aaron Wong (MSc student)



DIGGING DOWN TO THE GENES

Dr Liu and his team are also looking closely at genes implicated in lung injury and repair. A mouse model they have developed, which lacks a specific gene of interest, is proving key to this research. Dubbed XB130, this gene discovered by Dr Liu's lab is involved in a particular pathway (P13K/Akt) known to be important for the correct functioning of the cell cycle and

plays a role in the control of cell growth, proliferation and differentiation.

Thus, XB130 is important in lung epithelial repair and regeneration, a process crucial for donor lungs' survival after transplant. Also implicated in human tumorigenesis (the development of cancer), XB130 is clearly vital to the wider study of lung disease and therapy. A second gene has

also been identified as a particular interest to Dr Liu, coding for proteins involved in the mechanotransduction signalling pathway.

These molecular studies also link to nanoscale therapeutics. Disrupting specific protein-protein interactions with short peptides represents a new and exciting direction of drug development. The identification of specific genes and

Q&A

How did you become involved in lung research?

In 1980, when I was a medical student in Shanghai, I was a member of a small group of students to pilot biomedical research. We focused on ARDS (acute respiratory distress syndrome), a leading cause of death of patients who survived from trauma, shock, infection, or major surgery. Lung surfactant dysfunction was considered one of the major mechanisms. We worked tirelessly over the weekends, holidays and in the summer. The ample knowledge in the literature (mainly in English, which is a challenge on its own for Chinese students), the demand on critical thinking and technical details and the commitment to science made me fall in love with biomedical research. I continued to be a graduate student immediately after graduating from medical school. At that time, the number of graduate students in China was akin to the number of astronauts – few and far between. In three years, I designed and produced a prototype of modified Wilhelm balance, an electronic instrument to evaluate activities of surfactant. Following a protocol developed at the University of Toronto, I extracted bovine lung surfactant as a potential therapeutic for lung disease. I was then invited by Dr Goran Enhorning at the State University of New York at Buffalo to join his research team to continue research on surfactant therapies. Well, a long story for a short question.

What has made your collaboration with Dr Keshavjee so successful?

In 1994, I obtained my first research grant from MRC (Medical Research Council of Canada), now CIHR, to start my own

research. Dr Keshavjee finished his clinical fellowship training from Harvard University and returned to Toronto as a Surgeon Scientist. Recommended by Dr Arthur S. Slutsky, we joined our research labs together. Today, we have over 100 research trainees and staff in our team, including 12 PIs. I consider the collaboration between me and Dr Keshavjee to be one of the best examples of collaborative research and I truly believe this is very important for developing an effective translational research team. The most important point is the equal partnership between Clinicians and Basic Scientists. Dr Keshavjee is a great visionary leader in translational medicine. Today, Dr Keshavjee is the Surgeon-in-Chief at UHN, the largest research hospital in Canada. I am the Director of the Institute of Medical Science, the largest graduate training programme at the University of Toronto with over 600 faculty and 550 graduate students.

What do you think has been your greatest achievement so far?

I have been recognised as an international expert on Cellular and Molecular Mechanisms of Acute Lung Injury. My greatest achievement is reflected by the title of one of my research grants: Acute Lung Injury – from cellular mechanisms to molecular therapies. My lab is unique in that we use intracellular signal transduction pathways as potential therapeutic targets, nano-technology to formulate therapeutics, and then test them through a drug discovery pipeline. The collaborations with Dr Keshavjee enable us to translate our work directly into clinical practice.

How will your research improve patient outcomes?

their proteins as targets, the design and selection of short peptides, using nanoscale tools to deliver them into cells, and testing them through a drug discovery pipeline (including cells, small animal models for initial screening, large animal pre-clinical trials, and EVLP) is what sets Dr Liu's research apart – and has played key roles in much of his success to date.

Our work directly impacts the clinical outcome of transplant patients. First, several of our research studies have changed real clinical practice in lung transplant surgery. The awareness of ventilator-induced lung injury helped us to develop the Toronto protocol of EVLP. Using EVLP, we have already significantly increased the utilisation of donor lungs (up to 30% increase annually). New drugs/therapies (including lung surfactant) that we are working on will be tested in the clinic very soon. We are also developing rapid molecular diagnostic tools for donor organ assessments. A medical device for EVLP is on its way.

What advantages does your team have in developing that pipeline from bench to bedside?

The first advantage of our team is strong leadership. As I mentioned, Dr Keshavjee and I are strong academic leaders. We built one of the strongest translational research teams in Canada (perhaps in the world, in terms of lung transplant). The second feature is our multidisciplinary team. We have cellular and molecular biologists, nano-technologists, bioinformatics specialists and, critically, surgeon scientists. Many members of our team are international fellows. Graduate students take the lead on their own research projects. We also have excellent programme managers and technical support. The third reason is the enriched scientific collaboration – we proudly call it “the Canadian way”. We have close collaborations with basic scientists at the University of Toronto, researchers in other institutions, key industry partners, and scientists and clinicians all over the world.

Dr Liu has the right team, with the right collaborators, in the right location to make a big difference towards improving patient outcomes in ischemic reperfusion injury and lung transplantation. Already an established name in the medical research community in Toronto, his current research has the potential to breathe fresh air into lung therapies worldwide.

Detail

RESEARCH OBJECTIVES

Professor Liu's research looks at ischemia reperfusion-induced lung injury in lung transplantation, and the cellular and molecular mechanisms of acute lung injury.

FUNDING

- Canadian Institutes of Health Research (CIHR)
- Ontario Research Fund
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COLLABORATORS

Shaf Keshavjee (Toronto General Hospital Research Institute; Toronto General Hospital; University Health Network)

BIO

Mingyao Liu received his MD and MSc from The Second Military Medical University in China. He was a Research Assistant Professor at the SUNY Buffalo and then a postdoctoral fellow at SickKids Research Institute in Toronto. He has been a faculty member at the University of Toronto since 1994.

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