



INNOVATION IN HEALTHCARE WITHOUT BORDERS

THE DELEGATES; THE
DISCUSSIONS; THE AIMS:
WE PREVIEW THE 2012
CONFERENCE



EXCLUSIVES

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of Health Research

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A small matter of survival

Professor Victor Laubach and Dr Irving Kron describe the work they are conducting into the mechanisms of adenosine receptors in the prevention of ischaemia-reperfusion injury after lung transplantation

To begin, could you provide an overview of your research?

Ischaemia-reperfusion (IR) injury, an acute inflammatory reaction, remains a significant cause of morbidity and mortality after lung transplantation and also leads to an increased risk of developing bronchiolitis obliterans, a major cause of mortality beyond one year of transplantation. Our core objective is to define how to prevent such injury. Our current project focuses on defining the roles of adenosine receptors in IR injury and how we can exploit specific adenosine receptor agonists in its prevention.

How has your laboratory established that lung IR injury is dependent on macrophage and T cell activation by production of TNF-alpha and interleukin-17?

Our early studies with macrophage-depleted mice and TNF-alpha knockout mice demonstrated that macrophage-produced TNF-alpha contributes to lung IR injury. From this our research evolved into studies of innate immune responses during the reperfusion period. We have recently made an intriguing discovery that iNKT cells, a small subset of CD4+ T cells, and IL-17 are critical for lung IR injury, and we have confirmed the importance of IL-17 by showing that injury can be attenuated by therapeutic treatment with an IL-17 blocking antibody. Further studies have now established that iNKT cells play a pivotal role in initiating injury: we now know that iNKT cell-produced IL-17 activates various pulmonary cell populations such as macrophages and epithelial cells after lung reperfusion. These findings represent a paradigm shift in our understanding of the role of T cells in lung IR injury.

What is the significance of this discovery for addressing the high mortality rates associated with lung IR injury?

We now believe that activation of pulmonary iNKT cells is a critical early event after reperfusion, resulting in rapid IL-17 production and subsequent activation of many downstream inflammatory pathways. Therefore, if we can intervene to block this early event, we might effectively prevent IR injury and thus reduce mortality, not only acutely in lung transplant patients, but also chronically, by reducing the risk of rejection from bronchiolitis obliterans.

Can you describe the role of the adenosine 2A receptor (A2AR) in attenuating lung IR injury?

Adenosine is a retaliatory metabolite that serves as a protective agent with largely anti-inflammatory effects. Adenosine mediates its effects through binding to four different receptors: A1R, A2AR, A2BR and A3R. The A2AR, predominantly expressed on T cells, neutrophils and macrophages, is known to mediate potent anti-inflammatory actions by downregulating cellular inflammatory responses. Our laboratory has established that A2AR activation potently attenuates lung IR injury in a variety of animal models.

What progress have you made in studying the impact of specific adenosine receptor agonists and antagonists?

Our initial studies demonstrated clearly that infusion of A2AR agonist during reperfusion reduces IR injury in rabbit lungs. We then applied this to a more clinically relevant porcine lung transplant model and showed that infusion of A2AR agonist during reperfusion attenuates IR injury after transplant. We now have evidence that A2AR agonist does this largely by binding to receptors on T cells to prevent their activation and production of pro-inflammatory cytokines, such as IL-17.

This is in agreement with our other studies demonstrating a pivotal role for iNKT cells in lung IR injury. Current, unpublished results now suggest that A2AR agonists prevent the activation of iNKT cells via a mechanism involving the inhibition of reactive oxygen species production in these cells.

We also have new evidence suggesting that A1R and A3R agonists, and A2BR antagonist, are protective after lung reperfusion.

Our next goal is to initiate human clinical trials to test the efficacy of A2AR agonist in preventing primary graft dysfunction after lung transplantation as well as reducing the risk that patients will develop bronchiolitis obliterans.

Might your research also be applicable to other forms of IR injury?

This is truly one of the most exciting aspects of our research. In collaboration with Drs Okusa and French at the University of Virginia, we now know that A2AR agonists also attenuate IR injury in the kidney and heart. Other labs have demonstrated excellent results in liver and islet cell models of transplantation. We believe that our research on A2AR-mediated protection is very applicable to the transplantation of many different organs.



DR IRVING KRON (LEFT) AND PROFESSOR VICTOR LAUBACH (RIGHT)

Improving the prognosis for lung transplant patients

Research at the **University of Virginia** is delving into the roles of Adenosine Receptors in ischaemia-reperfusion injury in lungs in order to safeguard patients after transplantation

SINCE THE FIRST human lung transplant was performed nearly 50 years ago, thousands of people have had the operation. Worldwide, more than 1,600 lung transplants are carried out annually. Despite advances in organ harvesting, post-operative care and managing rejection, lung transplants statistically have the worst outcomes of all major organ transplant procedures: about 15 per cent of patients die within a month of the operation and only about 50 per cent survive beyond five years.

Compared with other organs, lungs are more vulnerable to injury and many potential donor lungs cannot be used. Waiting lists are long and many people die while waiting for the operation. The process of reintroducing blood (reperfusion) to the ischaemic donor lung after transplant often triggers ischaemia-reperfusion (IR) injury. Patients with lungs so affected are more likely to die within 30 days of surgery; even if they survive this initial recovery period, they are more likely to suffer complications later, including rejection. There are currently no clinically available therapies for preventing lung IR injury. Treatment strategies consist mainly of artificially maintaining

oxygenation and lung function after the injury has been sustained.

Research being carried out at the University of Virginia aims to establish viable therapies for prevention of IR injury, with the supplementary objective of discovering whether donor lungs can be protected prior to transplant, or can be reconditioned such that they become viable candidates.

THE KRON AND LAUBACH LABORATORIES AT THE UNIVERSITY OF VIRGINIA

Dr Irving Kron is a thoracic surgeon and was disturbed by the incidence of IR injury in his lung transplant patients. He joined forces with Professor Victor Laubach, a pure scientist trained in molecular, cell and pulmonary biology, to work together in exploring mechanisms and therapies of IR injury. They have worked as Principal Investigators on a variety of research projects over the last 15 years.

In the laboratory, Kron guides their research from a clinical perspective, directing the use of animal

models, and steering translational work. He also heads a hypothesis-driven research training programme for surgery residents, funded by the National Institutes of Health. Laubach directs most of the research including experimental design, collection and interpretation of data, and writing of grants and manuscripts.

Together, the duo are confident that the synergy of clinical experience and pure science is enormously beneficial to them: "Identification of therapeutic targets depends upon understanding the molecular and cellular mechanisms of the disease. Our research has filled important gaps in understanding the mechanistic causes of IR injury," asserts Laubach.

ADENOSINE RECEPTOR RESEARCH

Kron and Laubach's major goal is to develop strategies for preventing lung IR injury, and they believe that the identification of key early events that trigger inflammation in lungs and lead to injury will enable this.

They have already established that lung IR injury is dependent on CD4+ T cell and alveolar macrophage activation. Adenosine, a small molecule released by many cells during inflammation, has largely anti-inflammatory effects via binding to four different receptors: A1R, A2AR, A2BR and A3R.

Kron and Laubach are currently determining the roles of each of these adenosine receptors, establishing which receptors on which types of cells predominantly deliver anti-inflammatory effects, and consequently exploring how the mechanisms of receptor-mediated protection work. They have majored on researching the effects of A2AR: "Our overall hypothesis," explains Kron, "is that specific activation of A2ARs on CD4+ T cells provides protection from acute lung IR injury after transplantation."

Little is currently known about the role of other adenosine receptors in lung IR injury. However, as Laubach reveals, the project has uncovered that adenosine may exert harmful as well as protective effects: "The role of other adenosine receptors in injury appears to be somewhat complex. Although it is largely agreed that A1R and A3R are mainly anti-inflammatory, new evidence from our laboratory suggests that the A2BR is pro-inflammatory in the setting of lung IR".



UNIVERSITY OF VIRGINIA
MEDICAL CENTER AND
PEGASUS MEDICAL
HELICOPTER

INTELLIGENCE

ADENOSINE RECEPTOR GRANT

OBJECTIVES

This research aims to determine mechanisms of lung ischaemia-reperfusion (IR) injury after transplantation and develop therapeutic strategies to prevent such injury. The current project focuses on the therapeutic application of adenosine receptor agonists/antagonists to prevent IR injury. If successful, this research will translate to more lives saved of those patients on the lung transplant waiting list.

KEY COLLABORATORS

Joel Linden, PhD, La Jolla Institute for Allergy & Immunology

Mark Okusa, MD, University of Virginia Health System

Brent French, PhD, University of Virginia Health System

Tony Herring, Laboratory Manager, University of Virginia Health System

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DR IRVING KRON earned a BA from the University of Pennsylvania and received his MD from the Medical College of Wisconsin. He has been a Principal Investigator on over 10 research grants from the NIH and American Heart Association, among others, and has authored more than 360 scientific publications. He is also the Principal Investigator for an NIH-funded T32 Institutional Research Training Grant for Cardiovascular Surgery Residents.

PROFESSOR VICTOR LAUBACH earned his BS in Biology from the Pennsylvania State University and his PhD in Genetics from the George Washington University. He is the recipient of multiple NIH-funded grants, is an active member of the American Thoracic Society, and serves on several editorial boards including the American Journal of Respiratory Cell and Molecular Biology and the American Journal of Physiology Lung Cellular and Molecular Physiology.

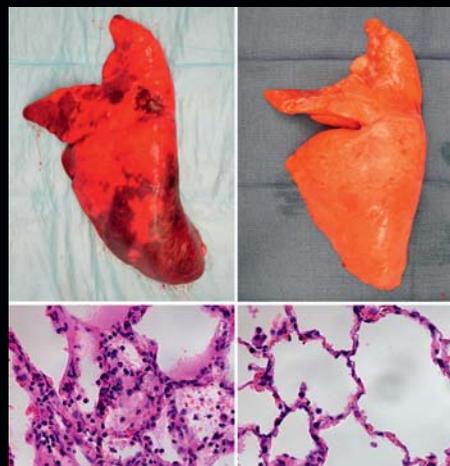
The Kron and Laubach laboratories are also currently determining whether the mechanisms of AZAR protection from IR injury involve several particular intracellular signalling molecules that regulate cell activities including gene expression, cell proliferation and survival. "Our laboratory has shown that NF- κ B and NADPH oxidase activities are increased in the lung after transplantation and that inhibition of either attenuates IR injury," observes Laubach. "We are now evaluating whether AZAR agonist-mediated inhibition of either NADPH oxidase or NF- κ B, or both, in T cells are critical mechanisms of its anti-inflammatory properties after reperfusion."

LUNG REHABILITATION RESEARCH

The first human lung transplant from a non-heart-beating donor, where the lung was perfused with an extracellular colloid solution using *ex vivo* lung perfusion, was performed in 2001. This novel technique is now being used for the assessment and potential reconditioning of marginal donor lungs.

One of the latest projects of the Kron and Laubach laboratories, funded by the Roche Organ Transplant Research Foundation in Switzerland, is testing the hypothesis that combining *ex vivo* lung perfusion with AZAR agonist treatment will considerably rehabilitate marginal lungs for successful transplantation. In this project, the researchers are using a porcine lung transplant model as well as evaluating

AZAR AGONIST TREATMENT (RIGHT) PROTECTS LUNGS AFTER TRANSPLANTATION



whether marginal human donor lungs can be similarly rehabilitated: "We believe that the therapeutic application of AZAR agonist using *ex vivo* lung perfusion could greatly increase the donor lung pool size, and so save many lives through reduced organ wait list times," enthuses Kron.

KEY KNOWLEDGE

Kron and Laubach recognise the significant contributions of their team efforts and value their role in nurturing hybrid medical scientists who approach clinical problems with research discipline. The pair's laboratories have now amassed a wealth of research studies related to their finding that AZAR agonist treatment substantially reduces lung IR injury after transplantation. Their recent studies add further details, exposing the precise mechanisms at work, and showing that AZAR agonists exert their protective effects mainly by activating AZARs on Natural Killer T cells, thus blocking IL-17 cytokine production after reperfusion has commenced.

They have recently shown that a single treatment of a donor lung with AZAR agonist, preceding harvest, also significantly protects the lung from incurring IR injury after transplantation. Their studies also suggest that *ex vivo* perfusion and AZAR agonist treatment of lungs from non-heart-beating donors rehabilitates donor lungs to perform relatively well after transplantation.

Among their various animal subjects, Kron and Laubach have used genetically altered mice, deficient in a single gene product, such as A2BR or AZAR, along with specific receptor agonists and antagonists in their research, and find this approach particularly effective. They are now eager to test the performance of AZAR agonist in trials with human lung transplant patients: "Our pre-treatment strategy could become a standard therapy for the prevention of IR injury after transplantation and perhaps lead to more specific, potent therapeutic strategies that have minimal side effects," predicts Kron.

Looking ahead, Laubach sees the research as contributing to the wider field of major organ transplantation: "Our results are very exciting because we feel that the protective effects of AZAR agonist can also be applied to other organs such as heart, kidney and liver," he enthuses.