Lung transplantation - lessons learned from experimental models

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Surgical Director, Lung Transplant Program
1st Lung Transplant
## Early experience: 1963 – 1974 (n = 36)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Type Tx</th>
<th>Survivor</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLD/Ca</td>
<td>Lt SL</td>
<td>18 d</td>
<td>Renal failure</td>
</tr>
<tr>
<td>CLD</td>
<td>Lt SL</td>
<td>8 d</td>
<td>Rejection; pneumonia</td>
</tr>
<tr>
<td>Bronchiectasis/TB</td>
<td>Lt LL</td>
<td>18 d</td>
<td>Rejection</td>
</tr>
<tr>
<td>Ca</td>
<td>Rt SL</td>
<td>5 h</td>
<td>Resp. failure</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Lt SL</td>
<td>7 d</td>
<td>Rejection; pneumonia</td>
</tr>
<tr>
<td>CLD/Ca</td>
<td>Lt LL</td>
<td>7 d</td>
<td>Rejection; alveolar hemorrhage</td>
</tr>
<tr>
<td>HCl pneumonitis</td>
<td>Lt SL</td>
<td>1 h</td>
<td>Resp. failure</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Lt SL</td>
<td>8 d</td>
<td>Rejection</td>
</tr>
<tr>
<td>PPH</td>
<td>Lt LL</td>
<td>3 h</td>
<td>Resp. failure; PGD</td>
</tr>
<tr>
<td>Trauma</td>
<td>Rt SL</td>
<td>2 d</td>
<td>Resp. failure</td>
</tr>
<tr>
<td>Ca</td>
<td>Lt SL</td>
<td>8 h</td>
<td>Resp. failure; bleeding</td>
</tr>
<tr>
<td>Paraquat</td>
<td>Lt SL</td>
<td>13 d</td>
<td>Resp. failure; rejection?</td>
</tr>
<tr>
<td>COPD</td>
<td>Lt SL</td>
<td>26 d</td>
<td>Rejection*; pneumonia</td>
</tr>
<tr>
<td>CHD/Eisenmenger</td>
<td>H-L</td>
<td>14 h</td>
<td>Resp. failure</td>
</tr>
<tr>
<td>COPD</td>
<td>Lt SL</td>
<td>6 d</td>
<td>Rejection; resp. failure</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Rt SL</td>
<td>10 mo</td>
<td>Rejection; pneumonia</td>
</tr>
<tr>
<td>CLD/pneumonitis</td>
<td>Lt SL</td>
<td>29 d</td>
<td>Rejection; resp. failure</td>
</tr>
<tr>
<td>CLD/Ca</td>
<td>Rt SL</td>
<td>14 d</td>
<td>Rejection; resp. failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
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<th>Survivor</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>LT SL</td>
<td>10 d</td>
<td>Rejection; resp. failure</td>
</tr>
<tr>
<td>COPD</td>
<td>Lt SL</td>
<td>10 d</td>
<td>Rejection; pneumonia</td>
</tr>
<tr>
<td>COPD/TB</td>
<td>Lt SL</td>
<td>11 d</td>
<td>Rejection; resp. failure</td>
</tr>
<tr>
<td>COPD</td>
<td>Lt SL</td>
<td>4 d</td>
<td>CVA; resp. failure</td>
</tr>
<tr>
<td>COPD</td>
<td>H-L</td>
<td>8 d</td>
<td>Pneumonia; resp. failure</td>
</tr>
<tr>
<td>COPD</td>
<td>BL</td>
<td>11 d</td>
<td>Rejection; dehiscence</td>
</tr>
<tr>
<td>COPD/TB</td>
<td>Rt SL</td>
<td>15 d</td>
<td>Dehiscence</td>
</tr>
<tr>
<td>IPF</td>
<td>Rt SL</td>
<td>2 mo</td>
<td>Abscess/fistula</td>
</tr>
<tr>
<td>Restrictive LD</td>
<td>Lt SL</td>
<td>1 mo</td>
<td>Pneumonia; resp. failure</td>
</tr>
<tr>
<td>COPD</td>
<td>H-L</td>
<td>23 d</td>
<td>Pneumonia; dehiscence</td>
</tr>
<tr>
<td>COPD</td>
<td>Rt SL</td>
<td>6 mo</td>
<td>PA fistula</td>
</tr>
<tr>
<td>COPD</td>
<td>Lt SL</td>
<td>15 d</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Rt SL</td>
<td>6 d</td>
<td>Pneumonia; resp. failure</td>
</tr>
<tr>
<td>COPD/Ca</td>
<td>Lt SL</td>
<td>1 d</td>
<td>Resp. failure</td>
</tr>
<tr>
<td>Paraquat</td>
<td>Rt SL</td>
<td>5 d</td>
<td>Paraquat toxicity?</td>
</tr>
<tr>
<td>CLD</td>
<td>Lt SL</td>
<td>OR</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>CLD</td>
<td>Lt SL</td>
<td>9 d</td>
<td>Gastric dilatation</td>
</tr>
<tr>
<td>COPD</td>
<td>Lt SL</td>
<td>2 d</td>
<td>Hyperacute rejection?; bleeding</td>
</tr>
</tbody>
</table>
Pioneer in Europe

Prof Dr F. Derom

14 November 1968, Gent, Belgium

Bronchial Dehiscence

Morgan, E 1982
Revascularization of ischemic bronchial grafts by omentopexy
Unilateral Lung Transplantation for Pulmonary Fibrosis

Toronto Lung Transplant Group

Abstract
Improvements in immunosuppression and surgical techniques have made unilateral lung transplantation feasible in selected patients with end-stage Interstitial lung disease. We report two cases of successful unilateral lung transplantation for end-stage respiratory failure due to pulmonary fibrosis. The patients, both oxygen-dependent, had progressive disease refractory to all treatment, with an anticipated life expectancy of less than one year on the basis of the rate of progression of the disease. Both patients were discharged six weeks after transplantation and returned to normal life. They are alive and well at 26 months and 14 months after the procedure. Pulmonary-function studies have shown substantial improvement in their lung volumes and diffusing capacities. For both patients, arterial oxygen tension is now normal and there is no arterial oxygen desaturation with exercise.

This experience shows that unilateral lung transplantation, for selected patients with end-stage interstitial lung disease, provides a good functional result. Moreover, it avoids the necessity for cardiac transplantation, as required by the combined heart–lung procedure, and permits the use of the donor heart for another recipient. (N Engl J Med 1986; 314:1140–5.)
Adult and Pediatric Lung Transplants

Number of Transplants by Year and Procedure Type

NOTE: This figure includes only the lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of lung transplants performed worldwide.
Freedom from BOS (n=1000)

Freedom from BOS (%)

84.0% (n=710)
54.3% (n=348)
38.2% (n=185)
12.2% (n=23)

Time from Transplant (years)
Experimental Lung Transplantation

- Large animals, Rats
  - Orthotopic Lung Transplantation
  - Heterotopic Tracheal Transplantation

- Mice
  - Heterotopic Tracheal Transplantation
  - Orthotopic Tracheal Transplantation
  - Bone Marrow Transplantation
    - Orthotopic Lung Transplantation
Vladimir Demikhov (1916-1998)

• “At the time of our experiments in 1946, we did not find a description of any intrathoracic transplantation in a warm-blooded animal.”

Shumacker HB, Ann Thor Surg 1994
Large Animals - Canine

• Dogs
  – Metras H (1950) CR Acad Sci (Paris)
  – Hardin CA and Kittle CF (1954) Science
    • Technical aspects
    • Bronchial anastomotic healing
    • Immunosuppression
Rat Orthotopic Lung Transplantation

• Species with well defined immunological backgrounds
• 1971: Sutured anastomoses in large rats (400-600 grams) (Asimacopoulouos PJ Transplant Proc)
• 1982: Technique refined for smaller rats (Marck KW, Ann Thor Surg)
• 1989: Cuff techniques (Mizuta T, JTCVS) – Shortening of procedure time, ischemic time - Reproducible
Heterotopic Tracheal Transplantation

Advantages:
- Lesions resemble OB
- Transgenics
- Reproducibility
- Technical ease

Disadvantages
- Not vascularized
- Not aerated
- Large airways

Mouse Lung Transplantation

Day 28

B6→B6

Balb→B6

Tx

Tx

AJRCMB 2007
Mouse Lung Transplantation

B6 → B6 Day 28

Balb → B6 Day 7

AJRCMB 2007
Allorecognition
Historical Perspective

• **HOMOGRAFT REACTION**

• “Sensitization to homograft takes place in two stages”
  – Fixed antigen in graft and leukocyte present in peripheral blood
  – Passage of primed leukocytes towards regional centers

Peter Medawar (1915-1987)
Historical Perspective

- Skin grafts are not rejected if they are placed on an island of recipient skin that had been separated from lymphatic drainage.

- Failure of the immune system to recognize the presence of antigen that does not reach host lymphoid organs.

Secondary Lymphoid Organs are **Essential** for Allograft Rejection

**Heart Transplants**

Rat Orthotopic Lung Transplantation – Acute Rejection

Lung Day 2

Heart Day 2

Prop J, Am J Path 1987
Histology

C3H → B6

Day 3

Cutting Edge J Immunol 2009
B6 CD11c-EYFP

CMTMR

CBA

Analysis 30 hrs
Allogeneic

Lung Graft

Cutting Edge J Immunol 2009
Lung Rejection in Absence of SLO

Day 7

Cutting Edge J Immunol 2009
Costimulation Blockade Prevents Acute Lung Rejection

*MR1 (d0) & CTLA4-Ig (d2)*

13 months
Tolerance Induction

Days post transplant

% Graft Survival

- Balb/c --- B6
- Balb/c --- B6 (LTx: Balb/c to B6 w CSB 30ds )
- CBA --- B6 (LTx: Balb/c to B6 w CSB 30ds )
Memory T cells are a Barrier to Transplantation Tolerance

Donor-Reactive CD8 Memory T Cells Infiltrate Cardiac Allografts Within 24-h Posttransplant in Naive Recipients

Allograft Rejection by Primed/Memory CD8$^+$ T Cells Is CD154 Blockade Resistant: Therapeutic Implications for Sensitized Transplant Recipients

Expansion of Memory-Type CD8$^+$ T Cells Correlates With the Failure of Early Immunosuppression Withdrawal After Cadaver Liver Transplantation Using High-Dose ATG Induction and Rapamycin

Transplantation, 2013
CD8 T Cells are Critical for Tolerance Induction

JCI 2014
CD8 T Cells Suppress Alloimmunity

JCI 2014
CD8 T Cells Induce Death of Responder T Lymphocytes

Gated on CD4^+CD45.1^+ T lymphocytes

%7-AAD

No CD8^+ T cells +Lung CD8^+ T cells +Spleen CD8^+ T cells

19.6 13.7 1.61 91.1 17 17.3

47.9 18.8 1.67 5.66 51.8 14

JCI 2014
CD8 Central Memory T Cells
CD8 Central Memory T Cells

BALB/c→B6 Cd8−/− + CD8+ CM T cells + CSB

BALB/c→B6 Cd8−/− + CD8+ EM T cells + CSB

TXP

ISHLTA grade

JCI 2014
Suppression by CD8 T cells
Depends on IFN-γ
Tolerance Depends on NO Production

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JCI 2014
Requirement for Chemokine Receptors

A CD8+ memory T cell infiltration into lung

B BALB/c→B6 Cdr8+/− + CD8+ Ccr7+/− T cells + CSB

C Relative expression

PTX No PTX
Intravital Two Photon Microscopy

- Quantitative measurement of leukocyte trafficking in deep vessels
- Track interstitial motility

LysM-GFP
655 nm Q-dots
CCR7 Mediates Synapse Formation
Current immunosuppression for lung transplant recipients needs to be reevaluated

Is induction therapy in lung transplantation deleterious?

Alemtuzumab in Lung Transplantation: An Open-Label, Randomized, Prospective Single Center Study

AJT 2014
Lung Allograft Acceptance is Associated with Lymphoid Neogenesis

Accepted Lung Graft

Native Lung

Mucosal Immunology, 2012
Lymphoid Neogenesis in Murine Cardiac Allografts Undergoing Chronic Rejection

Fady K. Baddoura, Isam W. Nasr, Barbara Wrobel, Qi Li, Nancy H. Ruddle, and Fadi G. Lakkis

Acutely and/or chronically rejected heart allografts

Am J Transplantation 2005
Tertiary lymphoid organs in renal allografts can be associated with donor-specific tolerance rather than rejection

Kathryn Brown, Steven H. Sacks and Wilson Wong
Role of inducible bronchus associated lymphoid tissue (iBALT) in respiratory immunity
Juan E Moyron-Quiroz, Javier Rangel-Moreno, Kim Kusser, Louise Hartson, Frank Sprague, Stephen Goodrich, David L Woodland, Frances E Lund & Troy D Randall

Nature Medicine, 2004

Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis
Javier Rangel-Moreno,1 Louise Hartson,1 Carmen Navarro,2 Miguel Gaxiola,2 Moises Selman,2 and Troy D. Randall1

1Trudeau Institute, Saranac Lake, New York, USA. 2Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico.

JCI, 2006
Inducible BALT

B6 → CBA (CSB) day 30
Dendritic Cells in iBALT
T cells interact with DCs in iBALT
CD4⁺Foxp3⁺ accumulate in iBALT
Lung Retransplantation

B6 → B6 (3 days) → B6 (day 30)
Lung Retransplantation

Mucosal Immunology, 2012
Heart Retransplantation

(a) Image of tissue sample
(b) Image of tissue sample
(c) Graph showing graft survival over days with different labels:
Dendritic cells are crucial for maintenance of tertiary lymphoid structures in the lung of influenza virus–infected mice

Corine H. GeurtsvanKessel,1,2 Monique A.M. Willart,3 Ingrid M. Bergen,1 Leonie S. van Rijt,1,5 Femke Muskens,1 Dirk Elewaut,4 Albert D.M.E. Osterhaus,2 Rudi Hendriks,1 Guus F. Rimmelzwaan,2 and Bart N. Lambrecht1,3

Induced bronchus-associated lymphoid tissue serves as a general priming site for T cells and is maintained by dendritic cells

Stephan Halle,1 Hélène C. Dujardin,1 Nadja Bakocevic,1 Henrike Fleige,1 Heike Danzer,1 Stefanie Willenzon,1 Yasemin Suezer,2 Günter Hämmerling,3 Natalio Garbi,3 Gerd Sutter,4 Tim Worbs,1 and Reinhold Förster1
CD11c^+ cells maintain tolerance
CD11c+ cells maintain tolerance
Conclusions

• Advances in clinical lung transplantation are aided by insights gained in experimental models
• Mouse models are good platform for mechanistic studies
• Early events after lung transplantation determine fate of the graft
Acknowledgments

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• Mohsen Ibrahim
• Jihong Zhu
• Tsuyoshi Takahashi
• Kelsey Toth
• Harold Steiner

Collaborators:
• Mark Miller
• Marco Colonna
• Steve Brody