Lung Transplantation—An Ongoing Evolution
<table>
<thead>
<tr>
<th></th>
<th>1983</th>
<th>1993</th>
<th>2003</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academy award best picture</td>
<td><img src="image1" alt="1983 Academy Award" /></td>
<td><img src="image2" alt="1993 Academy Award" /></td>
<td><img src="image3" alt="2003 Academy Award" /></td>
<td><img src="image4" alt="2017 Academy Award" /></td>
</tr>
<tr>
<td>Top song</td>
<td>Every Breath You Take -- Police</td>
<td>I Will Always Love You -- Whitney Houston</td>
<td>In Da Club - 50 Cent</td>
<td>Shape Of You Ed Sheeran</td>
</tr>
<tr>
<td>Transplants</td>
<td>Tom Hall. Nov. 7, 1983</td>
<td>667</td>
<td>1085</td>
<td>2057</td>
</tr>
<tr>
<td>1-year survival</td>
<td>‘87 1st year 33%</td>
<td>76.5%</td>
<td>84.1%</td>
<td>87.2%</td>
</tr>
<tr>
<td>5-year survival</td>
<td>16.7%</td>
<td>45%</td>
<td>56%</td>
<td>??</td>
</tr>
<tr>
<td>Indication for tx</td>
<td>IPF</td>
<td>&gt; 50% COPD or emphysema</td>
<td>&gt;50% IPF</td>
<td>LAS- mortality waiting and post tx</td>
</tr>
<tr>
<td>Waitlist</td>
<td>What waitlist</td>
<td>Time on list</td>
<td>Time on list, 3 mo for IPF</td>
<td>LAS- mortality waiting and post tx</td>
</tr>
</tbody>
</table>
More than 10,000 lung transplant recipients alive in the US
Changes in Who gets Transplanted

• LAS introduction in May 2005
• Dramatic shift from COPD/CF to IPF and sicker (ICU/ventilator/ECMO)
• Increasing use of ECMO, particularly ambulatory ECMO as bridge to transplant
• The over 65 population is dramatically increasing
Innovation and Transplant

- **1st decade** – experimental
- **2nd decade** – marked improvements in outcomes
- **3rd decade** – few centers develop mature processes - large volume
- **4th decade** – commoditization of transplant – reduced variability in outcomes, volumes

Gartner Hype Curve & Rogers's Diffusion of Innovations.
Greater variation between centers transplant rate vs survival

![Graph showing the relationship between transplant rate and 1-year survival. The graph indicates a higher variation between centers in transplant rate and survival rates.](image-url)
Stabilization of improvements in survival
Trends in Lung transplants

Age

Sex

Race

LAS

PRA

Diagnosis group

Year
Transplant Rates by age and diagnosis

- **Age**
  - 12-17
  - 18-34
  - 35-49
  - 50-64
  - 65+
  - All

- **Diagnosis group**
  - A
  - B
  - C
  - D

Graph showing transplant rates per 100 wait-list years by age and diagnosis group from 1998 to 2012.
Increasing age
Lung Transplant - DUMC

![Graph showing lung transplant data with age groups and percentages over years.](image)
Impact of Age on Survival – Age > 65

Duke
Age > 70 –

Impact of broadening selection criteria

P=0.0047
The aged as a different phenotype

• Greater infectious/cancer risk despite lower immunosuppression
  – Similar rejection
• Greater rates of organ failure– particularly renal
• Increased neuro-psychiatric complications
  – Delirium
  – Anxiety
  – Depression
• Autonomic dysfunction
  – Postural hypotension
Delirium and Survival

Survival based on post-op delerium

Time

Survival probability (%)

P = 0.2981
### Increasing severity of illness and use of ECMO

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th></th>
<th>2007</th>
<th></th>
<th>2012</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Pretransplant medical cond.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hospitalized: ICU</td>
<td>44</td>
<td>4.2</td>
<td>131</td>
<td>8.8</td>
<td>174</td>
<td>9.8</td>
</tr>
<tr>
<td>Hosp.: not ICU</td>
<td>51</td>
<td>4.8</td>
<td>127</td>
<td>8.6</td>
<td>171</td>
<td>9.7</td>
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<tr>
<td>Not hospitalized</td>
<td>960</td>
<td>91.0</td>
<td>1,223</td>
<td>82.6</td>
<td>1,389</td>
<td>78.4</td>
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<tr>
<td>Unknown</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>37</td>
<td>2.1</td>
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<tr>
<td><strong>On ventilator /ECMO at tx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vent + ECMO</td>
<td>3</td>
<td>0.3</td>
<td>7</td>
<td>0.5</td>
<td>35</td>
<td>2.0</td>
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<tr>
<td>Vent only</td>
<td>22</td>
<td>2.1</td>
<td>63</td>
<td>4.3</td>
<td>80</td>
<td>4.5</td>
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<tr>
<td>ECMO</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>0.2</td>
<td>21</td>
<td>1.2</td>
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<tr>
<td>Neither</td>
<td>1,030</td>
<td>97.6</td>
<td>1,408</td>
<td>95.1</td>
<td>1,635</td>
<td>92.3</td>
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<tr>
<td><strong>Procedure type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lobar</td>
<td>12</td>
<td>1.2</td>
<td>3</td>
<td>0.2</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Single</td>
<td>501</td>
<td>49.0</td>
<td>520</td>
<td>35.8</td>
<td>569</td>
<td>32.7</td>
</tr>
<tr>
<td>Bilateral</td>
<td>510</td>
<td>49.9</td>
<td>930</td>
<td>64.0</td>
<td>1,172</td>
<td>67.3</td>
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<tr>
<td><strong>Donor type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Deceased</td>
<td>1,043</td>
<td>98.9</td>
<td>1,478</td>
<td>99.8</td>
<td>1,770</td>
<td>99.9</td>
</tr>
<tr>
<td>Donation after brain death</td>
<td>1,042</td>
<td>98.8</td>
<td>1,469</td>
<td>99.2</td>
<td>1,749</td>
<td>98.8</td>
</tr>
<tr>
<td>Donation after cardiac death</td>
<td>1</td>
<td>0.1</td>
<td>9</td>
<td>0.6</td>
<td>21</td>
<td>1.2</td>
</tr>
<tr>
<td>Living</td>
<td>12</td>
<td>1.1</td>
<td>3</td>
<td>0.2</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Increasing use of ECMO bridge to Transplant
Outcomes and temporal trends among high-risk patients after lung transplantation in the United States

Timothy J. George, MD, Claude A. Beaty, MD, Arman Kilic, MD, Pali D. Shah, MD, Christian A. Merlo, MD, MPH, and Ashish S. Shah, MD

A

Survival (Percent)

- Highest LAS Quartile
- Ventilatory Support
- ECMO Support

P < 0.001

Number at risk
Highest LAS Quartile 1858
Ventilatory Support 525
ECMO Support 122

Time (Days)

B

Survival (Percent)

- Highest LAS Quartile
- Ventilatory Support
- ECMO Support

P = 0.004

Number at risk
Highest LAS Quartile 1367
Ventilatory Support 358
ECMO Support 52

Time (Days)

90 day conditional survival
High LAS

ECMO

vent
Center volume

Single vs. bilateral

Survival (Percent)

Time (Days)

P = 0.02

P = 0.10

P < 0.001
Ambulatory ECMO

Improved outcomes, perhaps better than bridging off a ventilator, decreased ICU, LOS and myopathy
Am J Respir Crit Care Med Vol 185, Iss. 7, pp 763–768, Apr 1, 2012
UNOS--Report the candidate’s assisted ventilation as “continuous mechanical ventilation”; and supplemental oxygen as FiO2 of 100%
Avalon Cannula Design
Avalon Cannula Design
Veno-Venous ECLS- Avalon

- Provides oxygenated pulmonary blood flow
- Needs functioning RV
- Avalon cannula provides excellent drainage and minimal mixing
- Requires imaging to place
Avalon Cannula Positioning
Cannulation Advantage: Ambulation

- Critical illness neuromyopathy
  - ICU associated weakness increases mortality, length of ICU stay\(^1\)
    - Risk factors include immobility, neuromuscular blockade
    - Days of mechanical ventilation are predictor on MV analysis
  - RCTs shows early mobilization of ventilated patients decreases ICU LOS and improves return to independent function\(^2,^3\)

Ambulation known to be important for lung transplant recipients
  – Preoperative strength predicts postoperative outcome\(^1\)
  – Duke Center for Living

Awake patients participating in rehabilitation on ECLS has been shown to be safe and associated with improved outcomes\(^2,3\)

Right internal jugular vein

Right axillary artery
Extracorporeal Membrane Oxygenation in Awake Patients as Bridge to Lung Transplantation

Thomas Fuehner¹, Christian Kuehn², Johannes Hadem³, Olf Wiesner³, Jens Gottlieb¹, Igor Tudorache², Karen M. Olsson¹, Mark Greer¹, Wiebke Sommer², Tobias Welte¹, Axel Haverich², Marius M. Hoeper¹, and Gregor Warnecke²

¹Department of Respiratory Medicine, ²Department of Cardiothoracic, Transplant and Vascular Surgery, and ³Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

A

Awake ECMO to LuTx group (n=26)

Secondary intubation (n=7)

→ Died on ECMO (n=6)

→ Died after LuTx on ICU (n=3)

→ Discharged from hospital (n=3)

→ Not intubated (n=19)

→ Died on ECMO (n=3)

→ Successful bridging to LuTx (n=4)

→ Discharged from hospital (n=13)

B

Intubation to LuTx group (n=34)

Died before LuTx (n=16)

→ Secondary ECMO (n=4), Secondary ECLA (n=14)

→ Successful bridging to LuTx (n=24)

→ Died after LuTx on ICU (n=12)

→ Discharged from hospital (n=12)

Survival

A

logrank p=0.02

Time (days)

B

logrank p=0.05

Time (days)
Changing role and outcomes – ECMO bridge to transplant

Figure 1.
### Single Center Experience – VV ECLS

<table>
<thead>
<tr>
<th></th>
<th>Mech vent (n=34)*</th>
<th>Awake ECLS (n=26)*</th>
<th>Columbia (n=15)^</th>
<th>Duke (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to Tx (%)</td>
<td>24 (71)</td>
<td>20 (77)</td>
<td>10 (67)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Death post-Tx (&lt;1 yr)</td>
<td>12 (50)</td>
<td>4 (20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ambulation</td>
<td>0</td>
<td>0</td>
<td>5 (33)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>LOV post-Tx</td>
<td>37 (1-72)</td>
<td>14 (0-64)</td>
<td>n/a</td>
<td>8 (2-25)</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>39 (4-74)</td>
<td>18 (1-69)</td>
<td>22 (18-33)</td>
<td>11 (5-25)</td>
</tr>
</tbody>
</table>

*Fuehner, AJRCCM, 2012
^ Javidfar, JTCVS, 2012
Duke Experience – VV ECLS – Bridge to Lung Transplant
So Doc explain to me, if I have a lung disease that is so bad that I’m going to die, how is it that one lung is better than 2??

If we only had magic wands and pixie dust
Single vs. Bilateral-- No randomized trial data

- Potential of 2 recipients benefiting
  - US 2/3rds are discarded
- Smaller incision- less restrictive defect
- Less early resource utilization
  - Blood
  - LOS
  - OR
- Quicker

- Better post transplant spirometry
- Better functional capacity
  - Modest improvements in 6 minute walk
  - Peak VO2
- No native lung left behind
  - Infection
  - Cancer
  - Mediastinal shift
  - Shunt
Incision and choice of procedure impacts post transplant respiratory mechanics

- Impact of incision on respiratory restrictive defect
  - Sternotomy
  - Anterolateral thoracotomy
  - Posterolateral thoracotomy
  - Bilateral thoracotomy
  - Clamshell
Impact of Anesthesia in post thoracotomy restriction

Figure 2. Evolution of pain score after operation. a, Statistically significant difference (P<0.05) between epidural and control group; c, statistically significant difference (P<0.05) between epidural and cryo group.

Figure 4. Evolution of oral analgesics consumption after operation. a, Statistically significant difference (P<0.05) between epidural and control group; b, statistically significant difference (P<0.05) between cryo and control group; c, statistically significant difference (P<0.05) between epidural and cryo group.

Figure 3. Mean percentage changes in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) on the second and seventh postoperative days. Error bars indicate SD. *Significantly different to Epidural Group, P < 0.05.
Fig 1A
Transternal thoracotomy in 4th intercostal space

Fig 2
Thoracotomy along inframammary crease
Clamshell in Men
Clamshell in Women
Diaphragm Retraction
IPF/Small Chest

Stitch in Fibrous portion of diaphragm

Pulled through at the nadir of the pleural cavity
Heart Herniation
Advantages of Exposure

Intra-pericardial exposure of pulmonary veins/artery

Left side exposure—no LA appendage
Right Sided Exposure of Both Sides

Mobilization of LA/PA

Posterior Dissection of Left PV’s
Extraction of mediastinal lymph nodes

Plane immediately behind the pericardium

Exposure of carina, left bronchus – hemostasis
Pre-Implant Closure

Posterior pleural tubes and Intercostal closure
Use of Pennington Clamps

29. Connection of the pulmonary venous system (2). The posterior row of the pulmonary venous anastomosis is completed.
Closure

Use of # 7 wire

Simple mid-sternum

Wide Figure of 8 through body of sternum and around ribs–approximately 2 figure widths

Tension Free– Bailey Retractors
Who is it that the trauma/wait time of the bilateral procedure outweighs the benefit of having 2 lungs

• IPF—era effect
• Aged (moving target)
• Obese??
• Frail
• PH

Amazing how many times the UNOS data set can be used and come up with different conclusions
Stage bilateral-One at time

2009-2013
192 patients with ILD

Low/Normal Risk (Minimal Comorbidities, Young) 74 (39%)
BOLT

High Risk (Age > 65, Coronary Artery Disease, Frail) 106 (55%)
SOLT

Unable or unwilling to undergo a second transplant
No 2nd Stage

Staged Contralateral SOLT 12 (6%)
Case Control Kaplan-Meier Survival Curves Staged Bilateral v. BOLT v. SOLT

Survival (%)

Years

BOLT 24 19 18 12 9 5
SOLT 24 19 15 10 7
Staged Bilateral 12 12 11 5 1 1

Log-rank test: p=0.205
Lung Transplant Priorities

• Not enough organs
• Unreliable organ performance
  – PGD
• Inadequate long-term allograft performance
• Toxicity of Immunosuppression
  – Infection, Cancer, Organ Failure
Never enough donors!
Perspective

**Lung Transplantation**
- 3rd leading cause of death > 149,205 per year
- 2000 lung transplants/year
- Large centers perform 100
- Organ utilization of 17%

**Liver Transplantation**
- 12th leading cause of death 27,555
- 6300 liver transplants/year
- Large centers perform 200-300/year
- Organ Utilization of 87%
Ex vivo perfusion of human lungs

Pre - Treatment

Post Treatment
Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.
**EVLP Status**

- Three Center Experience with Clinical Normothermic Ex Vivo Lung Perfusion
  - M. Cypel,1 C. Aigner,2 E. Sage,3 T. Machuca,1 A. Slama,2 M. Stern,3 W. Klepetko,2 A. Chapelier,3 S. Keshavjee.1
  
  1University of Toronto, Toronto, Canada; 2Vienna University, Vienna, Austria; 3Hopital Foch, Paris, France.

  - Incidence of PGD 3 at 24h and 72h were 7% and 5 % respectively
  - Thirty-day mortality was 4% ;proportional survival at 1 year was 88%.
  - 82.5% utilization after EVLP

- Normothermic Ex Vivo Lung Perfusion as an Assessment of Marginal Donor Lungs – The NOVEL Lung Trial
  - P.G. Sanchez,1 R.D. Davis,2 F. D’ovidio,3 M.J. Weyan,4 P.C. Camp,5 E. Cantu III,6 B.P. Griffith.1
  
  1Cardiac Surgery, University of Maryland, Baltimore, MD; 2Cardiac Surgery, Duke University, Durham, NC; 3Surgery, Columbia University, New York, NY; 4Surgery, University of Colorado, Aurora, CO; 5Thoracic Surgery, Brigham and Women’s Hospital, Boston, MA; 6Cardiac Surgery, University of Pennsylvania, Philade

  - 54% utilization
  - Thirty-day mortality 3%
  - HDE approval August of 2014
EVLP strategies

• Use of the currently unused lungs
  – Some of the 83% from heart-beating donors
  – DCD

• Use of the currently unusable lungs
  – Organ resuscitation

• Changing the overall donor paradigm
  – Maastricht class 1 and 2
**New Technology**

**Maastricht classification**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Place of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dead on arrival or dead &quot;in the field&quot;</td>
<td>Outside hospital</td>
</tr>
<tr>
<td>2</td>
<td>Unsuccessful resuscitation</td>
<td>In hospital ward, ICU, ER</td>
</tr>
<tr>
<td>3</td>
<td>Elective withdrawal of ventilatory support</td>
<td>In ICU or OR</td>
</tr>
<tr>
<td>4</td>
<td>Cardiac arrest while brain dead</td>
<td>In ICU or OR</td>
</tr>
</tbody>
</table>

Table 1. classification of NHBDs. The vast majority of NHBDs are Category 1.

**Chronic Lower Respiratory Tract Diseases** 142,943 in 2012 CDC

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>n</th>
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<tbody>
<tr>
<td>sudden cardiac</td>
<td>400,000</td>
</tr>
<tr>
<td>CV disease</td>
<td>157,000</td>
</tr>
<tr>
<td>accidents, all</td>
<td>106,000</td>
</tr>
<tr>
<td>MVA's</td>
<td>44,000</td>
</tr>
<tr>
<td>firearms</td>
<td>750</td>
</tr>
<tr>
<td>suicide</td>
<td>30,600</td>
</tr>
<tr>
<td>by firearms</td>
<td>17,000</td>
</tr>
<tr>
<td>homicide</td>
<td>17,000</td>
</tr>
<tr>
<td>by firearms</td>
<td>11,600</td>
</tr>
<tr>
<td>Total sudden deaths</td>
<td>784,000</td>
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</table>
Functional repair of human donor lungs by IL-10 gene therapy


biomimetic culture of human lung lobe
Changes in PGD—Lung Tx Outcome Group

Am J Respir Crit Care Med Vol 187, Iss. 5, pp 527–534, Mar 1, 2013

Any Donor Smoking

Donor Smoking
>20 pack-years

Reperfusion FiO₂
21-40%
40-100%

Recipient BMI
<18.5
18.5-25
25-30
>30

Pulmonary Hypertension
Normal
Mild
Moderate
Severe

Cardiopulmonary Bypass Use
Yes
No

PRBC Transfusion Volume
None
<1 L
>1 L

Gender and Parity
Female with 1 Pregnancy
Female with 2+ Pregnancies
Female with No Pregnancy
Male

Center

Standardized PGD Incidence

TABLE 3. UNADJUSTED ASSOCIATION OF GRADE 3 PGD AT 48 OR 72 HOURS WITH 90-DAY AND 1-YEAR MORTALITY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk in Those with PGD</th>
<th>Risk in Those without PGD</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-d mortality</td>
<td>23%</td>
<td>5%</td>
<td>4.8 (3.3–7.0)</td>
<td>18% (12–24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-yr mortality</td>
<td>34%</td>
<td>11%</td>
<td>3.0 (2.3–3.9)</td>
<td>22% (15–30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Chronic Allograft Dysfunction

- Nomenclature Changes
- Lack of Significant Impact
Chronic Lung Allograft Dysfunction (CLAD) BOS vs RAS

Bilateral lung or heart-lung transplant recipients who survived > 3 months with sufficient follow-up data (n = 493)

FEV1 < 80% baseline

excluded

CLAD (n = 169)

TLC < 90% baseline

BOS (n = 109)

FEV1 ≥ 80% baseline

No CLAD (n = 312)

FEV1 decline unrelated to graft dysfunction (n = 12)

exclude

Insufficient TLC data for phenotype determination (n = 13)

RAS (n = 47)
ADULT LUNG TRANSPLANTS
Kaplan-Meier Survival by Era
(Transplants: January 1988 - June 2010)

1988-1995 (N=5,949): 1/2-life = 3.9 Years; Conditional 1/2-life = 7.0 Years
1996-2003 (N=12,632): 1/2-life = 5.3 Years; Conditional 1/2-life = 7.9 Years
2004-6/2010 (N=17,715): 1/2-life = 5.9 Years; Conditional 1/2-life = NA

1988-95 vs. 1996-2003: p < 0.0001
1988-95 vs. 2004-6/2010: p < 0.0001
1996-2003 vs. 2004-6/2010: p < 0.0001

N at risk = 1,055
N at risk = 192
N at risk = 585
Environmental Exposure Hypothesis

- Aspiration—GERD, oro-pharyngeal dysfunction
- Pollution
Lung Transplantation -- Unique characteristics

- No systemic arterial circulation
- Exposed to the external environment
- Host defenses markedly affected
  - Poor mucociliary clearance
  - Denervated -- no cough reflex
Role of Aspiration Injury in OB

![Graph showing the impact of aspiration injury on FEV1 post Fundoplication and Re-TX.]
Role of fundoplication/aspiration in development of BOS

Bilateral Lung Transplant Recipients

Early Anti-reflux Surgery (n=29)
-pH Study, No Anti-reflux Surgery (n=41)
+pH Study, No Anti-reflux Surgery (n=124)
Abrogation of GERD/Aspiration Injury by Fundoplication

A One year  

B Peak

% Predicted FEV₁

p=0.003

NO GERD  GERD  FUNDO

NO GERD  GERD  FUNDO

p=0.001
Pollution and Transplant Outcome

Figure 1  Unadjusted Cox regression in patients after lung transplantation classified according to whether they lived within 171 m of a major road (n=96, lowest tertile, red line) or more than 171 m from a major road (n=192, blue line). BOS, bronchiolitis obliterans syndrome.
Pollution and Transplant Outcome

![Graphs showing hazard ratios and attributable fractions for BOS and mortality.](image)

<table>
<thead>
<tr>
<th>Distance to major road, m</th>
<th>Hazard ratio (95% CI) for BOS</th>
<th>Attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>800</td>
<td>1.04 (1.02-1.06)</td>
<td>3.8%</td>
</tr>
<tr>
<td>600</td>
<td>1.09 (1.04-1.14)</td>
<td>8.2%</td>
</tr>
<tr>
<td>400</td>
<td>1.17 (1.04-1.28)</td>
<td>14.7%</td>
</tr>
<tr>
<td>200</td>
<td>1.34 (1.14-1.58)</td>
<td>25.4%</td>
</tr>
<tr>
<td>150</td>
<td>1.43 (1.17-1.74)</td>
<td>30.0%</td>
</tr>
<tr>
<td>100</td>
<td>1.57 (1.22-2.02)</td>
<td>36.3%</td>
</tr>
<tr>
<td>50</td>
<td>1.88 (1.32-2.66)</td>
<td>46.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distance to major road, m</th>
<th>Hazard ratio (95% CI) for mortality</th>
<th>Attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>800</td>
<td>1.05 (1.00-1.09)</td>
<td>4.8%</td>
</tr>
<tr>
<td>600</td>
<td>1.11 (1.00-1.23)</td>
<td>9.8%</td>
</tr>
<tr>
<td>400</td>
<td>1.20 (1.00-1.45)</td>
<td>16.9%</td>
</tr>
<tr>
<td>200</td>
<td>1.39 (1.01-1.90)</td>
<td>27.8%</td>
</tr>
<tr>
<td>150</td>
<td>1.47 (1.01-2.14)</td>
<td>31.9%</td>
</tr>
<tr>
<td>100</td>
<td>1.60 (1.02-2.52)</td>
<td>37.2%</td>
</tr>
<tr>
<td>50</td>
<td>1.83 (1.02-3.30)</td>
<td>45.4%</td>
</tr>
</tbody>
</table>

*Figure 2*: Adjusted hazard ratio (with 95% CI, the grey area) for the incidence of bronchiolitis obliterans syndrome (BOS) and mortality in patients after lung transplantation, with 1000 m as reference. Hazard ratios were adjusted for sex, age, type of transplantation (single or double lung transplantation), infection with cytomegalovirus (CMV) and non-CMV infections, acute rejections, a factor reflecting time trend and social economic status. A corresponding table is given with HRs (95% CI) and the attributable fractions for the given distances.
Tolerance Trials

- Combined Immunodeficiency Disorder with Bronchiectasis
- Haplo-identical *cadaveric* donor—5/10 antigen match
- Lung transplant followed 3 months later by BMT
  - CD3 and CD19 depletion
  - Rituximab, Alemtuzumab, ATGAM, Hydroxyurea, a single dose of Thiotepa, and a single fraction of TBI
- Tolerant—no immunosuppression, no allograft rejection, immunocompetent
Lung allograft function
Reconstitution of T cell immunity
REPOSITORY TABLE 2.

Cytokine secretion by donor T cells. Bioplex assay from day 5 supernatants of mixed lymphocyte cultures as presented in Fig 2.

<table>
<thead>
<tr>
<th>Source of EBV/LCL stimulators</th>
<th>Mean values</th>
<th>Patient</th>
<th>Mother</th>
<th>3rd Party</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation (CPM)</td>
<td>1,725</td>
<td>46,514</td>
<td>62,617</td>
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</tr>
<tr>
<td>IL-2 (pg/ml)</td>
<td>&lt; 1</td>
<td>7.6</td>
<td>13.9</td>
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<tr>
<td>IL-6 (pg/ml)</td>
<td>1.1</td>
<td>2.5</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>IL-13 (pg/ml)</td>
<td>0.2</td>
<td>9.6</td>
<td>39.4</td>
<td></td>
</tr>
<tr>
<td>IL-17 (pg/ml)</td>
<td>0.2</td>
<td>1.4</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>IFNγ (pg/ml)</td>
<td>12.1</td>
<td>60.9</td>
<td>63.5</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Lung transplantation continues to grow—
  – Remains a severe gap between those who might benefit and the number of transplants performed
• Transplant recipients are older/sicker
• Outcomes are better
• Too much variability between programs
• Chronic allograft dysfunction is still a major obstacle
Thank You!