Refurbishing Centers in Lung Donation: is it the future?

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Disclosures

• Founding Partner:
  • XOR Labs Toronto Inc.
• XVIVO Perfusion – Research support and clinical trial
• United Therapeutics – Research support and clinical trial
• Xenios/Fresenius – Research support and investor in XOR Labs Toronto Inc
Models of Ex vivo Organ Perfusion

- What do we mean by ex vivo organ perfusion?
- What is the current state of ex vivo organ perfusion for lung?
- Different devices for performing EVLP
- Different models for delivery of care
Ex vivo Organ Perfusion: Taking Transplantation to the Next Level

→ A Precision Medicine Approach to Organ Resuscitation and Repair
→ Engineer “super-organs”
TORONTO EX VIVO LUNG PERFUSION (EVLP) SYSTEM

Gas for Deoxygenation
86% N₂, 8% CO₂, 6% O₂

Red: Venous (Oxygenated) perfusate
Blue: Arterial (Deoxygenated) perfusate
Perfusate: Acellular Steen Solution

Perfusion: 40% CO
Ventilation: 7cc/kg, 7BPM, PEEP 5, FiO₂ = 21%

Manipulate Preservation Temperature as Required
According to Organ / Clinical Needs:
Hypothermia ↔ Normothermia

• Time to accurately assess, diagnose
• Opportunity to treat, recover, repair
• Opportunity to reassess, confirm results
• Optimize organ preservation and Tx processes

→ improve utilization
→ precision medicine
→ predictable outcome
→ safety
The “Organ Repair Center”

- Lung
- Heart
- Liver
- Kidney
HELP II TRIAL

CLINICAL TRANSPLANTATION OF EX VIVO PERFUSED LUNGS
N = 638 Clinical EVLP to date

Toronto General Hospital OR
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.
Patient Survival for EVLP vs non-EVLP lung transplants
Toronto Lung Transplant Program Annual Growth
1991-2018

2000-2006
~100% increase
ECD era

2006-2012
Plateau
mean 93.5

2012-2018
100% increase
EVLP era
Number of Transplanted Lungs Assessed on EVLP

1983 – 2018

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Number of transplanted lungs assessed on extracorporeal lung perfusion (EVLP) from 1983 to 2018.
Toronto Lung Transplant Program Activity
1983 – 2019

212 lung transplants in 2019
1.4% operative mortality
Potential Ex vivo Treatment Strategies

- Perfusion
- Gene Therapy
- Drugs
- Cell Therapy
- Energy Devices
- Immuno-cloaking
- Biological
- Inhaled Gases
Systems to perform ex vivo perfusion of the lung and heart
The Future of Organ Transplantation = Organ Repair Centers
The Future State of Organ Transplantation

Organ Retrieval

Organ Repair Center

Transplant

Transplant

Transplant

Transplant

Transplant

Transplant

Transplant
Commercial Devices for EVLP

Models to Provide Clinical Ex vivo Lung Perfusion

1. Do it yourself – small center

2. Do it your self large center

3. Service provider – someone does it for you
The TGH “Organ Repair Center”

Lung  Heart
Liver  Kidney
Extended Preservation Time with Ex Vivo Lung Perfusion

• Normothermic EVLP allows for prolonged Total Preservation Time (TPT)
• Includes TWO periods of protective Cold Ischemic Times (CIT1 and CIT2)

Towards Elective Lung Transplantation: Outcome of Transplantation of Lungs Preserved More Than 12h

How we do it: Process at TGH

- Staff surgeon makes initial telephone assessment
- Fellows do on-site assessment, reporting and procurement
- Decision about the use of EVLP jointly made with fellow and surgeon
- Lungs recovered with LPD flush - cold static preservation for transport before and after EVLP
- EVLP performed at TGH by Ex Vivo Lung Specialists (EVLS, OPS)
- Some EVLP performed at third party Organ Perfusion Center for US lungs
Current Resources and Manpower Arrangements at TGH

• 6 surgical fellows for procurement
• 3 OPS (Organ Perfusion Specialists) with 50% commitment to clinical EVLP and 50% to the thoracic lab for research EVLP
• One Organ Perfusion Lab in TGH OR (building 2 more)
• Supplemented with research fellows from the lab (1 at each EVLP case)
Addressing multiple simultaneous EVLP needs: Call schedule now has first and second call

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Roles and Responsibilities at TGH

- OR nurses set up surgical table
- Perfusionist sets up circuit
- RT checks the ventilator
- Xray technician takes CXR at 1 and 3 hours
- EVLP Specialist primes circuit, attaches cannula and repairs LA if required
- EVLP Specialist monitors, adjusts ventilation, including recruitment protocols, bronchoscopy and blood gas analysis, hourly assessment and reporting
- OR nurse returns for “closing” count
Tom,

The general situation was stable. All the parameters were similar with the previous hour. Both lower lobes were little heavy, but were soft, no consolidation. Mild red color in the bottom area of the lungs, especially in RUL. Airway was clean. Deflation was normal, RLL was little slow compared to other lobes.

Parameters: 1H/2H/3H
PaP: 5/6/5
LaP: 4/4/4
Ppeak: 15/14/14
Pplat: 12/11/11
Pmean: 8/8/8
Cdyn: 82/86/84
Cstat: 124/137/133
Delta PO2: 519/522/550
Glu: 8.4/6.7/5.5

CXR: mostly clear

Manyin
Reporting: At 3 hours surgeon reviews images and parameters with the OPS
Implementation of High Volume Clinical EVLP: The Toronto Model

- EVLP is playing an increasing role in lung transplantation at TGH
- Requires a large team, resources and significant volume of cases to achieve excellent results

- It is not just increased donor availability in our region: lung transplantation rates increased significantly in our program (doubled) while other organ transplant rates did not…

- EVLP enabled us to utilize donor lungs with multiple risk factors, address logistical challenges and safely increase lung transplant activity (100%).
How do we scale this system wide?
EVLP will enable optimization of organ management in specialized centers: A lesson from the history of blood transfusion

- Unprocessed whole blood transfusion in the battlefield
- Processed blood transfusion in individual hospitals
- Standardized, centralized collection, processing, storage, distribution
- Optimized utilization
  - Separation of components for specific patient needs (RBC, platelets, plasma, cryo etc.)

Scale up, Achieve Cost and Utilization Efficiencies

Management of Blood Products: The Evolutionary Path
Can we apply these concepts to the management of donor organs for transplantation?
The Future State of Organ Transplantation

Organ Retrieval

Organ Repair Center

Transplant
Transplant
Transplant
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Transplant

Models to Provide Clinical Ex vivo Lung Perfusion

1. Do it yourself – small center

2. Do it your self large center

3. Service provider – someone does it for you
Successful Emergent Lung Transplantation After Remote *Ex Vivo* Perfusion Optimization and Transportation of Donor Lungs

C. H. Wigfield\textsuperscript{a, b}, M. Cypel\textsuperscript{b}, J. Yeung\textsuperscript{b}, T. Waddell\textsuperscript{b}, C. Alex\textsuperscript{a}, C. Johnson\textsuperscript{a}, S. Keshavjee\textsuperscript{a} and R. B. Love\textsuperscript{a}

Organ Repair Laboratory
Toronto General Hospital April 2011:

The 1\textsuperscript{st} “Service Provider”
28,000 ft² facility designed to meet the latest standards for operating rooms.

Six procedure rooms with equipment prep area, pathology lab, material storage, and administrative areas.

At full capacity, will be capable of over 1,800 lung assessments and extended preservation procedures per year.
LB1 Organ Repair Laboratory and Control Center
STUDY SITES - APR 2019

Planned Transplant Center Study Sites

1. Indiana University
2. University of Maryland
3. UPMC
4. Loyola University Chicago
5. Cleveland Clinic
6. University of Michigan
7. Duke University
8. Inova Fairfax
9. Newark Beth Israel
10. Washington University St. Louis
11. Johns Hopkins
12. New York University
13. Mayo Clinic Florida
14. Vanderbilt University
15. OPEN
16. OPEN

ACTIVE SITES
PENDING SITES
LB-2 (Jacksonville Florida) and LB-3 (Phoenix Arizona)
Lung Bioengineering, United Therapeutics and Mayo Clinic

• Commissioned Aug 22, 2019

• Business continuity for LBE:
  – IT redundancy
  – Interchangeable staffing
  – Direct lungs to LB1(SS) or LB2 (JAX) based on location, workload and center need
Organ Repair Laboratories in North America
(Lung Repair Centers)

Toronto ON
Jacksonville FL
Silver Spring MD
Donor Lung

Clinical and functional pre-assessment

Rapid diagnostic bioprofiling

Transplant

Transport to recipient

Confirm organ optimization (functional and bioprofile)

Apply ex vivo repair strategies

Define organ optimization and repair requirements

Precision Medicine for the Organ
The Organ Management and Transplantation Network

Donor Hospital

Organ Repair Center

Transport

Transplant Hospital

LTx Diagnostics

LTx Diagnostics

LTx Diagnostics