The Future of Transplantation
Personalized Medicine for the Organ:
AT WHAT COST?

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University of Toronto
Founding Partner and Chief Scientific Officer:
- Perfusix Canada Inc.
- Perfusix USA Inc. (Lung Bioengineering /UT)
- XOR Labs Toronto Inc.

XVIVO Perfusion – Research support and clinical trial

United Therapeutics – Research support and clinical trial
My Journey Through Innovation

1. Opportunities – the field, the environment

2. Innovations

3. My path through the academic environment, institution, departmental priorities, philanthropy, commercialization pathway

4. Changing the Ecosystem
Career Path

- Thoracic Surgeon – Surgeon Scientist – Univ of Toronto
- Academic path at UofT: Assistant → Assoc → Full Professor, Division Chair Thoracic Surgery UofT
- Division Head, Surgeon in Chief, University Health Network
- Grant funding, Publications, Awards
- Director Thoracic Surgery Research Laboratory → 70 members
- Director, Toronto Lung Transplant Program – clinical, academic and innovation leader
- Chief Scientific Officer Perfusix Canada, Perfusix USA and XOR Labs Toronto
THE LATNER THORACIC RESEARCH LABORATORIES
THE TORONTO LUNG TRANSPLANT TEAM
TGH WORLD FIRSTS...

Single Lung Transplant 1983

Bilateral Lung Transplant 1986

Lung Transplant for Cystic Fibrosis 1988
A Method for Safe 12 Hour Pulmonary Preservation.

Low Potassium Dextran preservation solution (Perfadex\textsuperscript{R}) improves lung function after human lung transplantation

Standard Approach to Donor Organ Management
3 Fundamental Problems with the Current Approach to Donor Organ Management

1. Cold flush preservation has been the cornerstone of the success of organ transplantation…but, cold hinders the possibility of active metabolic processes and repair.

2. Conceptual focus has been on slowing down death, rather than on facilitating recovery and regeneration.

3. Find out how the organ works AFTER we implant it.
IMPROVING OUTCOMES IN TRANSPLANTATION: ORGAN RESUSCITATION AND REPAIR
TORONTO EX VIVO LUNG PERFUSION (EVLP) SYSTEM

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

Leukocyte filter

Membrane
(De)oxygenator

XVIVO Chamber with Lungs

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

Cypel/Keshavjee J Heart Lung Transplant 2008;
27(12):1319-25.
HUMAN EX VIVO LUNG PERFUSION

The
Toronto
Lung Transplant
Program
HELP II TRIAL
CLINICAL TRANSPLANTATION OF EX VIVO PERFUSED LUNGS
N = 246 Clinical EVLP to date

Toronto General Hospital OR
Ontario Donors vs. LTx/Year
1991-03/2016 (ytd)

Number of Donors

Number of LTx

Year

LTx/Year

Deceased Donors (ON)

28%
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.
Outcomes with Clinical EVLP

K-M Survival Plot; EVLP (Yes/NO); Redo Excluded; N=699 (143+556)

Surviving

Years Post-Tx

p=0.956 (Log-Rank)
Toronto EVLP Timeline of Development

- **2005**
  - Concept Development & Study Design

- **2006**
  - Equipment Troubleshooting
  - **1st Animal Experiment**

- **2007**
  - **1st Human Transplant**
  - Human Trial Design: Researchers, Ethics board, patients

- **2008**
  - Completion of Trial and Health Canada Application

- **2010**
  - Approved for clinical use

- **2012**
  - Reimbursement

- **2012**

- **2005**
  - Toronto EVLP

- **2006**

- **2007**

- **2008**

- **2009**

- **2010**

- **2012**

**Timeline Events**

- 2005-2006: Development and study design.
- 2007-2008: Equipment troubleshooting and animal experiments.
- 2008: Human trial design involving researchers, ethics board, and patients.
- 2010: Completion of trial and application to Health Canada.
- 2012: Approval for clinical use and reimbursement.

**Supporting Organizations**

- Health Canada
- OHTAC
- MOH

**Additional Information**

- 1st Patient transplanted with Toronto EVLP system
- Timeline of Development
- University Health Network
Freedom from Chronic Rejection (CLAD)
(EVLP of high risk NDDs)

P = 0.03

No. at risk

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Cost Benefit Analysis of Ex vivo Lung Perfusion Therapy
Potential Gains

• Save more lives
• Healthcare cost saving opportunities:
  • Care of end stage lung disease patients – at home, multiple admissions, in hospital, on artificial support
  • Transplant hospitalization – better outcomes – shorter ICU stay, shorter hospital stay, less complications
  • Improved long term outcomes – less chronic rejection, better Quality of Life
  • Benefit to society – back to family, back to work
Gene Therapy with Adenoviral Vectors

1. Preparation of replication-defective adenoviral vector containing gene of interest (red)

2. Binding of vector to specific receptors

3. Receptor-mediated endocytosis

4. Breakdown of viral capsid and transfer of dsDNA to nucleus

5. Episomal gene expression

6. Expression of therapeutic mRNA and protein

Gene Therapy scheme:
- Cytosol
- Nucleus
- Genomic DNA
- Vector DNA
- mRNA
- Protein
- IL-10
FUNCTIONAL REPAIR OF HUMAN DONOR LUNGS BY EX VIVO IL-10 GENE THERAPY

Delivery of IL-10 by EVLP Ad Gene Therapy to injured human donor lungs resulted in improved lung function.

Lentiviral Gene Therapy
Long Term Intra-Graft Low Level Gene Expression

Ex vivo lung repair of damaged donor lungs using cell-based therapy with Mesenchymal Stem Cells
Treatment Strategies

- Perfusion
- Gene Therapy
- Cell Therapy
- Inhaled Gases
- Drugs
- Biological

Immuno-cloaking
How do we translate the knowledge and scale up ex vivo organ repair worldwide?

- Transplant Center - Centric Model

Diagram:

- Transplant
- Perfusion

Organ Procurement

- Transplant
- Perfusion

- Transplant
- Perfusion
Another World First…

Case Report

Successful Emergent Lung Transplantation After Remote Ex Vivo Perfusion Optimization and Transportation of Donor Lungs


Am J Transplant 2012
How will we apply and scale up Organ Repair clinically?

Organ Repair Hub Model

[Diagram showing the Organ Repair Center connected to multiple transplant options through organ procurement.]
THE “ORGAN REPAIR CENTER”

Lung

Heart

Liver

Kidney
The Future of Organ Transplantation

XOR
How do we put this all together?

- Advanced organ management
- Advanced diagnostics
- Advanced therapy
- Devices to support organs
- Staff to deliver treatment
- Implications for allocation, transport and distribution of organs
The History of Blood Transfusion
The History of Blood Transfusion

Unprocessed whole blood transfusion in the battlefield

Processed blood transfusion in individual hospitals

Optimized utilization
Separation of components for specific patient needs (RBC, platelets, plasma, cryo etc.)

Standardized centralized collection, processing, storage, distribution
Quality control: SOP’s, infection control, shelf life, inventory, distribution, safety standards, tracking

Management of Blood Product – The Evolutionary Path

Ability to scale up, achieve cost and utilization efficiencies
Can we apply these concepts to the management of donor organs for transplantation?
THE FUTURE STATE…

Organ Repair Hub Model
“The Organ Hub”
The First Lung Repair Center in the World
(Lung Bioengineering Inc.)
LB1 - Lung Bioengineering OR and Control Center
Certified Ex-Vivo Lung Specialist
Cross-Discipline Skill Sets

| Perfusion | RT | Surgical | Other Sub-Specialties | Certified Ex-Vivo Lung Specialist |
Perfusix – Lung Bioengineering
Lung Restoration Center
Remote Surgeon Data Interface
PX2 (Jacksonville Florida) and PX3 (Phoenix Arizona) - Perfusix, Lung Bioengineering, United Therapeutics and Mayo Clinic
Organ Repair Laboratories in North America (Lung Restoration Centers)

- Toronto ON
- Phoenix AZ
- Silver Spring MD
- Jacksonville FL
Opportunities and Challenges

• Doing it for the right reason
• Scientific and medical credibility
• Track record
• Continued research and development
• Philanthropic machine at UHN → enabler
• National Grants (CIHR, CFC, Genome Canada, Canada First Research Excellence Fund etc.)
• Partnership with University Health Network
• Other partners – investors
• Making a business case
• Patent lawyers, IP protection, royalties, licencing
• We will transform how transplantation is practiced...
Challenge:

HOW will we transform the way transplantation is practiced?
UNDERSTANDING THE TRANSPLANT ECOSYSTEM IN CANADA AND USA...
Organ Allocation

- How will this affect organ allocation?
- If a center turns down a lung, do they have “first rights” to the organ after it is repaired?
- Where does responsibility for function of the repaired organ stop and start?
- How is it different from what we currently/used to do?
- How should TGLN or UNOS address allocation of EVLP lungs?
- What about crossing the border for organ repair?
- UNOS Thoracic Committee on EVLP
Who will do what... and who will pay?

- Transportation of the organ
- EVLP – who is qualified to perform
- “Organ Perfusion Specialists” – training, accreditation
- How to regulate? Is all “EVLP” the same?
- It’s a new industry...
- Who will pay for usual organ retrieval and allocation aspects?
- Who will pay for newly introduced costs related to ex vivo organ treatment?
Steps to Personalized Medicine for the Organ

DONOR LUNG

Clinical Assessment

Excellent

Fails

Current Practice

TRANSPLANT

No Transplant
Personalized Medicine for the Organ

DONOR LUNG

Clinical Assessment
- Fails
  - Suitable
    - Rapid Bioprofiling
      - Fails… or Could be Improved
        - Ex vivo Repair Strategies
          - Reassess
            - Fails
              - No Transplant

Diagnostic Accuracy, Confirmation, Safety
Personalized Medicine and the Ex vivo Organ Repair Center Concept

• An unprecedented opportunity to:
  – Improve the number, quality and durability of organs for transplant
  – Manufacture and distribute “super organs”
  – Improve efficiency and safety of transplant process

• Spin off benefits from this technology… in vivo perfusion treatment for other lung disease, cancer, bioreactors to repair and regenerate organs

• A lot has to change in the transplant ecosystem – allocation, distribution, organ management, clinical practice

• Opportunities and challenges will vary in different jurisdictions

• Will have implications to multiple aspects of the transplantation ecosystem – we will have to change the way we practice…
The Toronto Lung Transplant Program