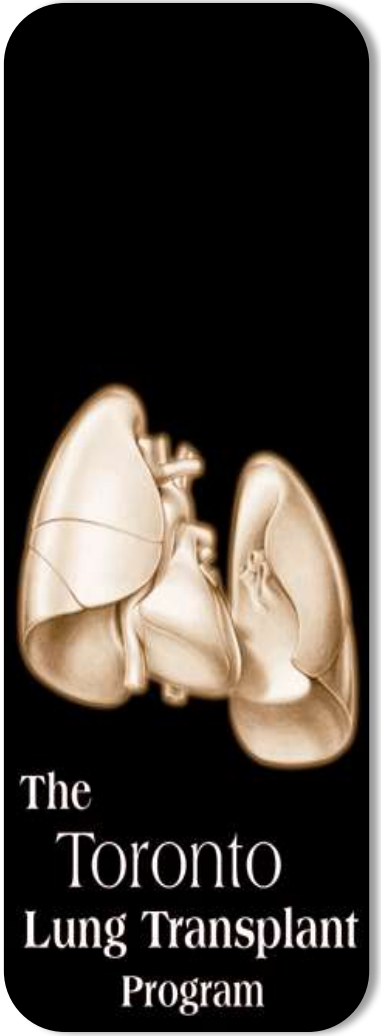
Doctors of Thoracic Surgery

UHN



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

Shaf Keshavjee OC O Ont. MD MSc FRCSC FACS

Director, Toronto Lung Transplant Program
Surgeon-in-Chief, University Health Network
James Wallace McCutcheon Chair in Surgery

Professor, Division of Thoracic Surgery and Institute of Biomaterials and Biomedical Engineering,
Vice Chair for Innovation, Department of Surgery
University of Toronto

Disclosure

- 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

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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.

J Thorac Cardiovasc Surg 1989; 98:529-34.
Keshavjee SH, Yamazaki F, Cardoso P, McRitchie DI, Patterson GA, Cooper JD.

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

Fischer S, Matte-Martyn A, dePerrot M, Waddell T, Sekine Y, Hutcheon M, Keshavjee S. *J Thorac Cardiovasc Surg 2001; 121(3): 594-596*

Standard Approach to Donor Organ Management

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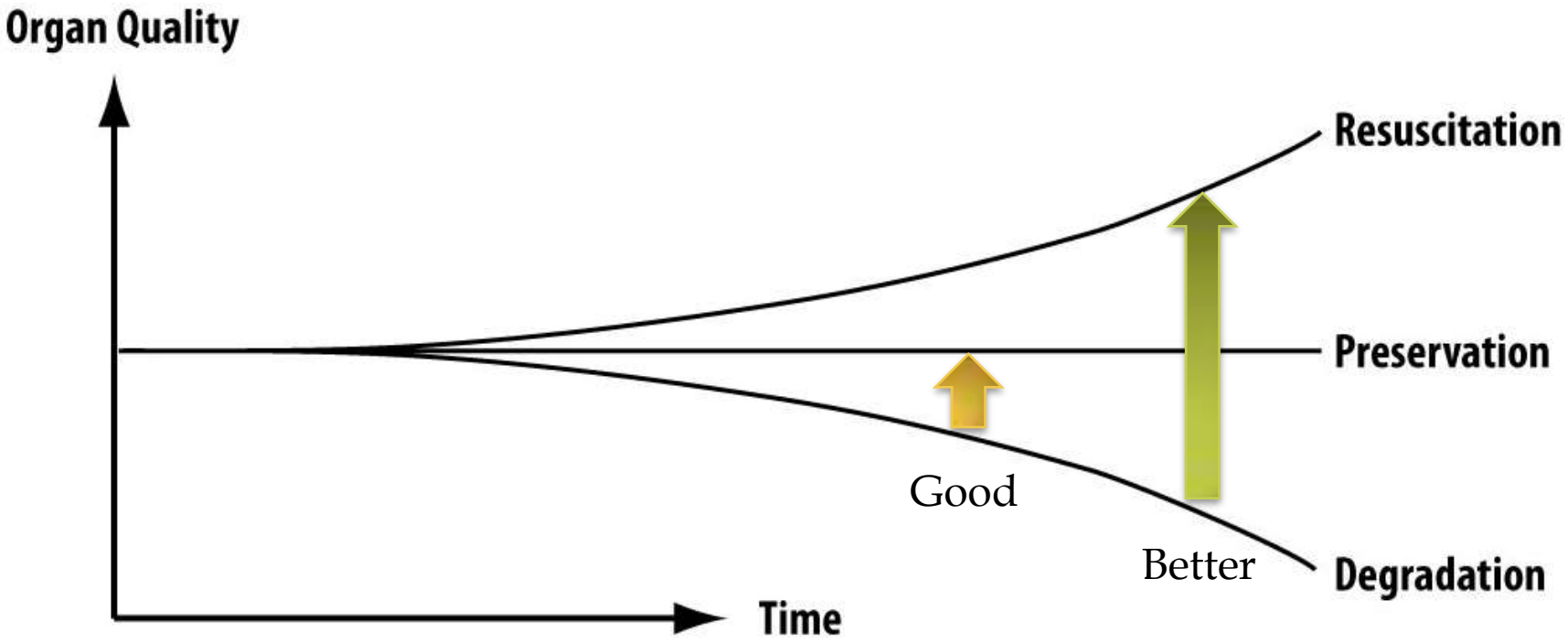
3 Fundamental Problems with the Current Approach to Donor Organ Management

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

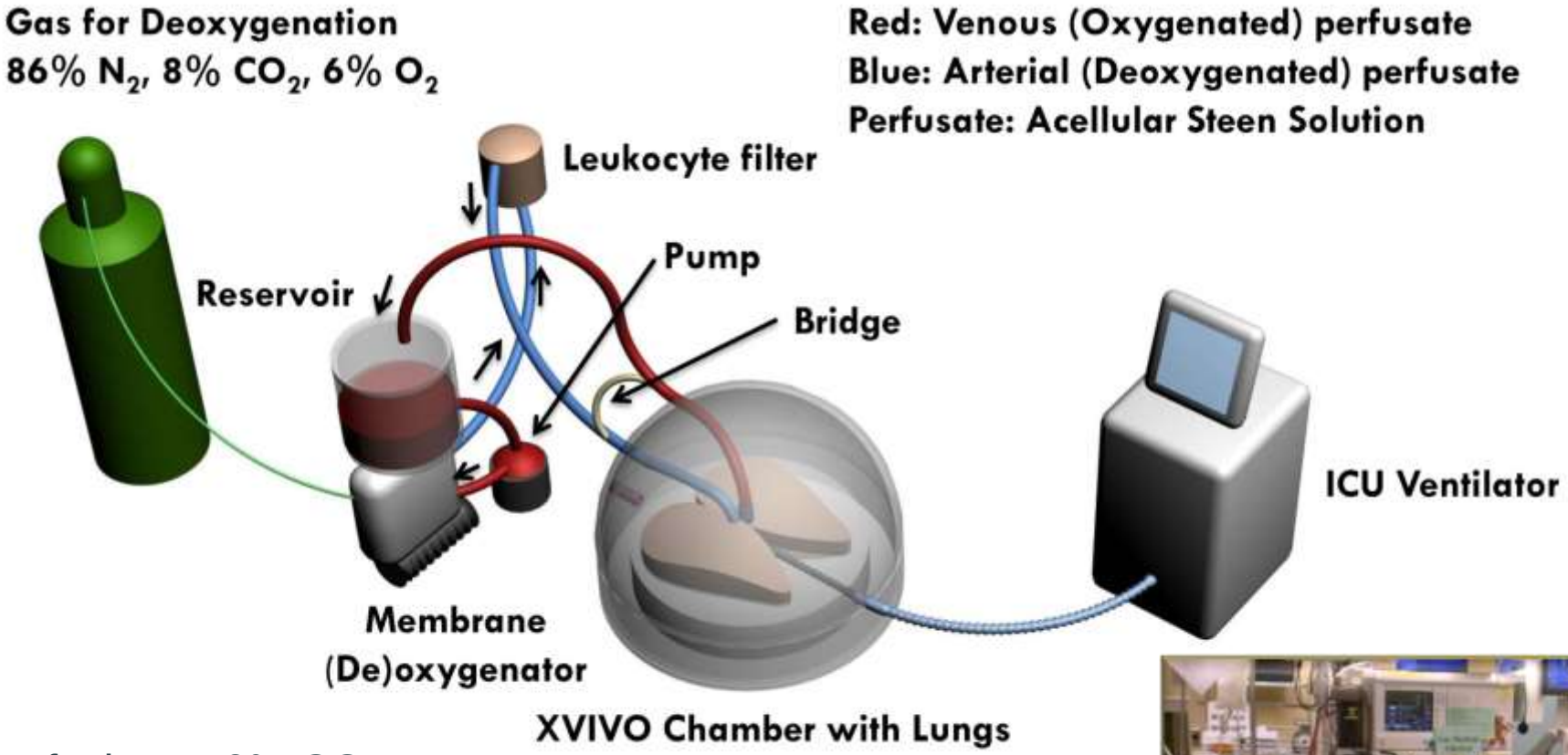
2. Conceptual focus has been on slowing down death, rather than on facilitating recovery and regeneration

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



Perfusion : 40% CO
Ventilation: 7cc/kg, 7BPM, PEEP 5, FiO_2 = 21%

Cypel/Keshavjee J Heart Lung Transplant 2008; 27(12):1319-25.

Human Ex Vivo Lung Perfusion

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HELP II TRIAL

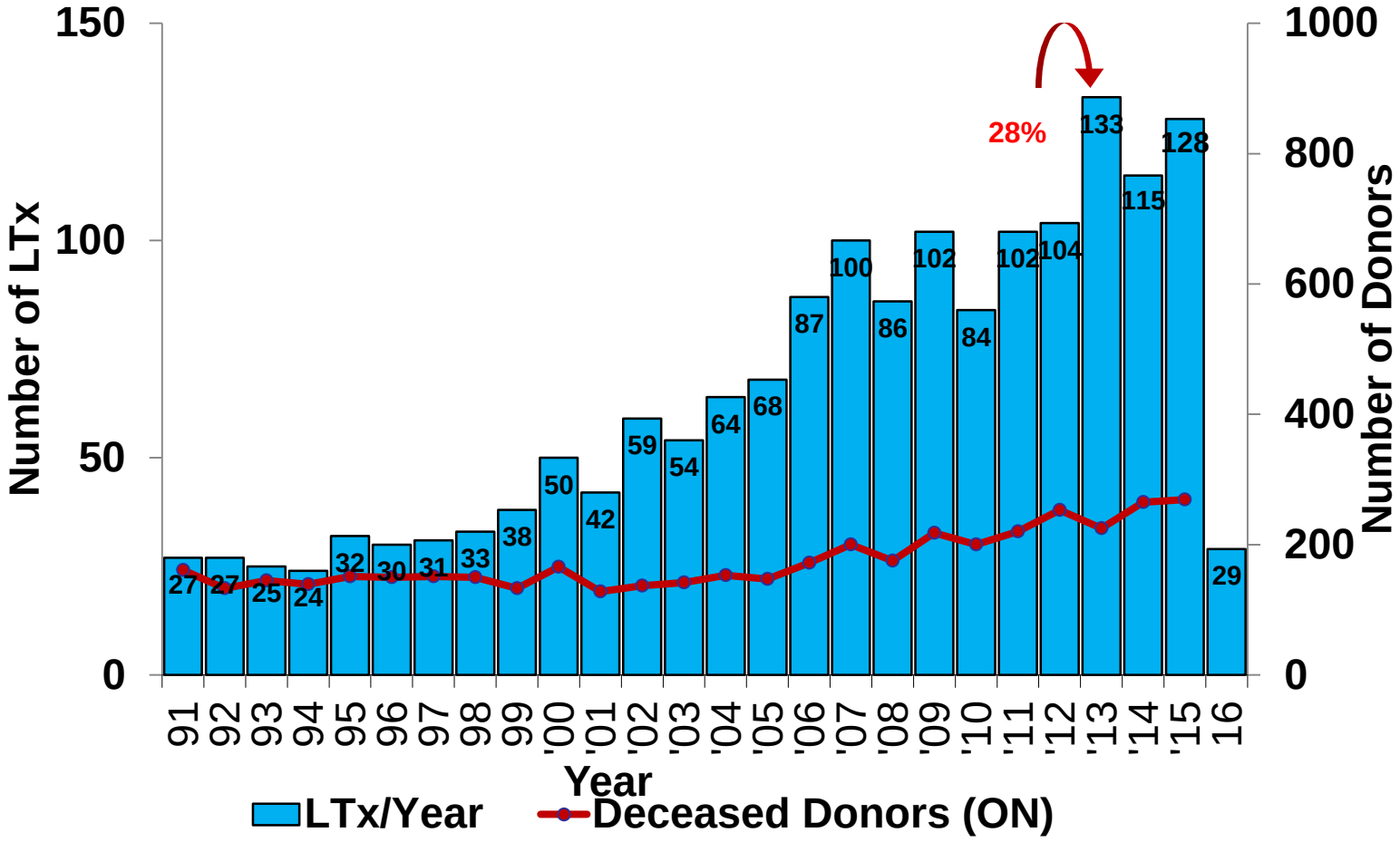
CLINICAL TRANSPLANTATION OF EX VIVO PERFUSED LUNGS

N = 246 Clinical EVLP to date

Toronto General Hospital OR

Ontario Donors vs. LTx/Year

1991- 03/2016 (ytd)



UHN Toronto Lung Transplant Program

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

April 14th 2011, vol. 364, no. 15, pp. 1431-1440.

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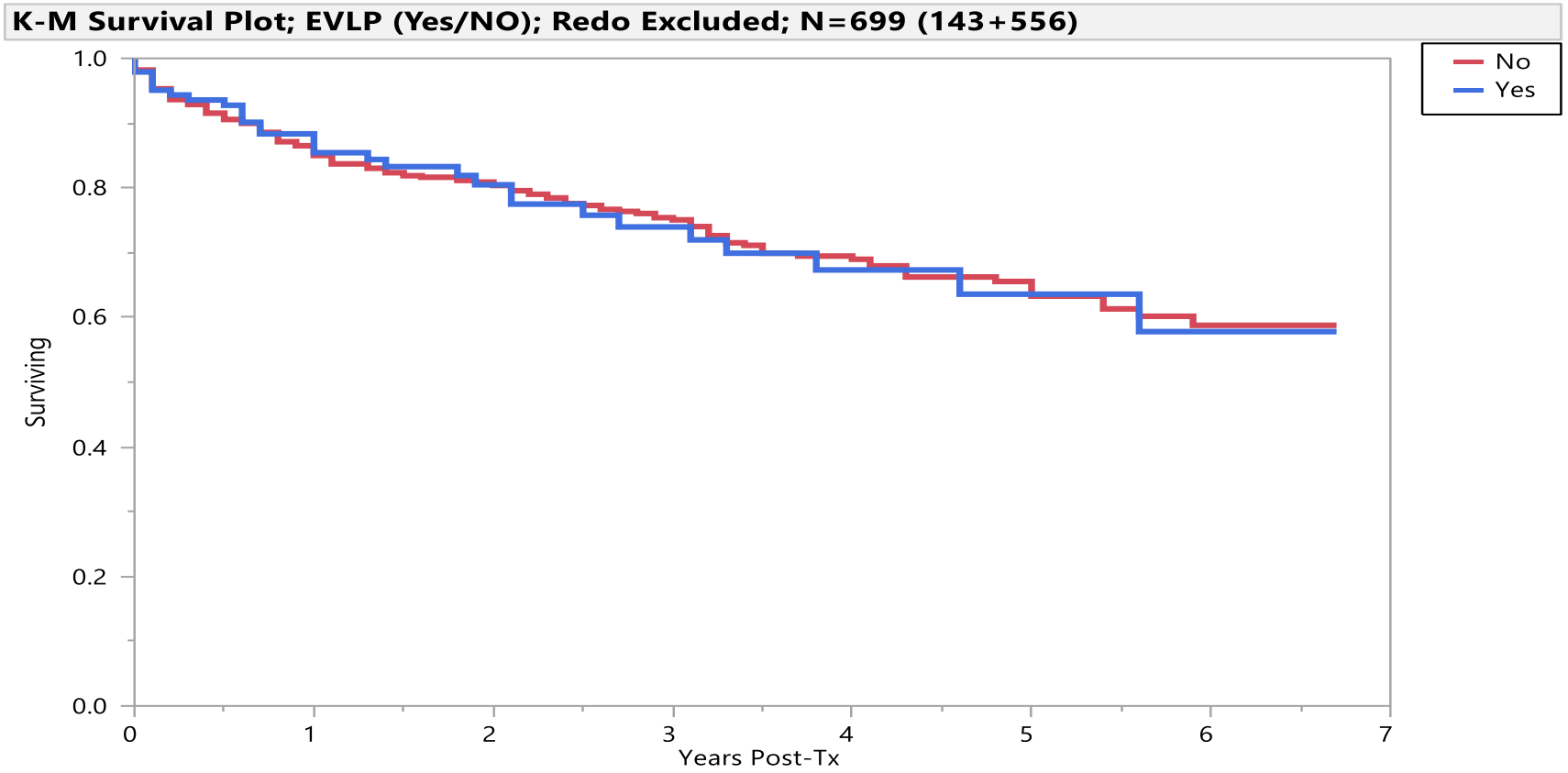
Outcomes with Clinical EVLP



p=0.956 (Log-Rank)

1st Patient transplanted with Toronto EVLP system

Toronto EVLP Timeline of Development

2005 – Concept Development & Study Design

2005 – Equipment Troubleshooting

2006 – 1st Animal Experiment

2007 – Human Trial Design:
- Researchers,
- Ethics board, patients

2008 – 1st Human Transplant

2010 – Completion of Trial and Health Canada Application

2012 – Approved for clinical use
- ✓ Health Canada
- • FDA (2014)

2012 – Reimbursement
- ✓ OHTAC
- ✓ MOH

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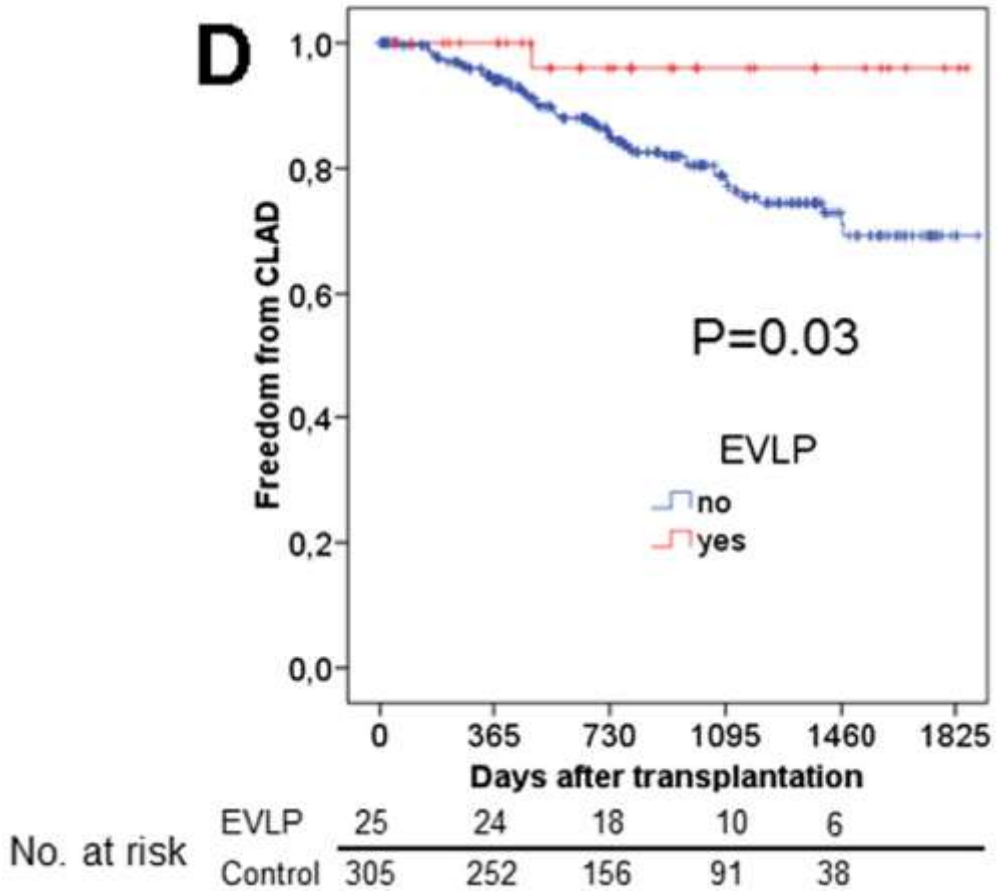
Freedom from Chronic Rejection(CLAD)

(EVLP of high risk NDDs)



Tikkanen / Singer, JHLT 2015

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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

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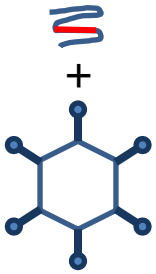
Gene Therapy with Adenoviral Vectors



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

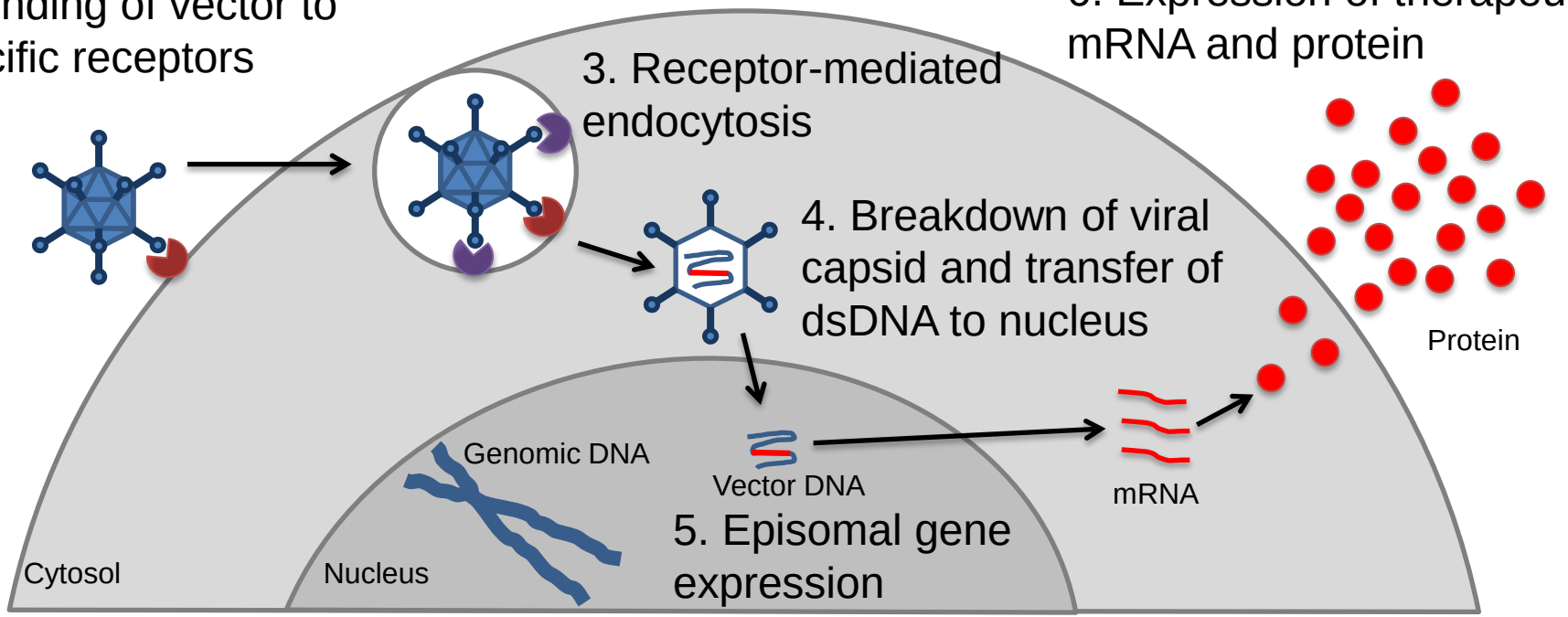
IL-10

2. Binding of vector to specific receptors

3. Receptor-mediated endocytosis

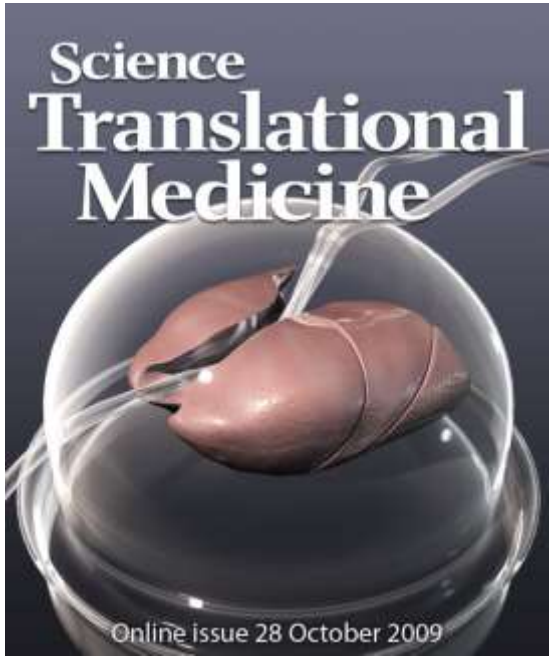
4. Breakdown of viral capsid and transfer of dsDNA to nucleus

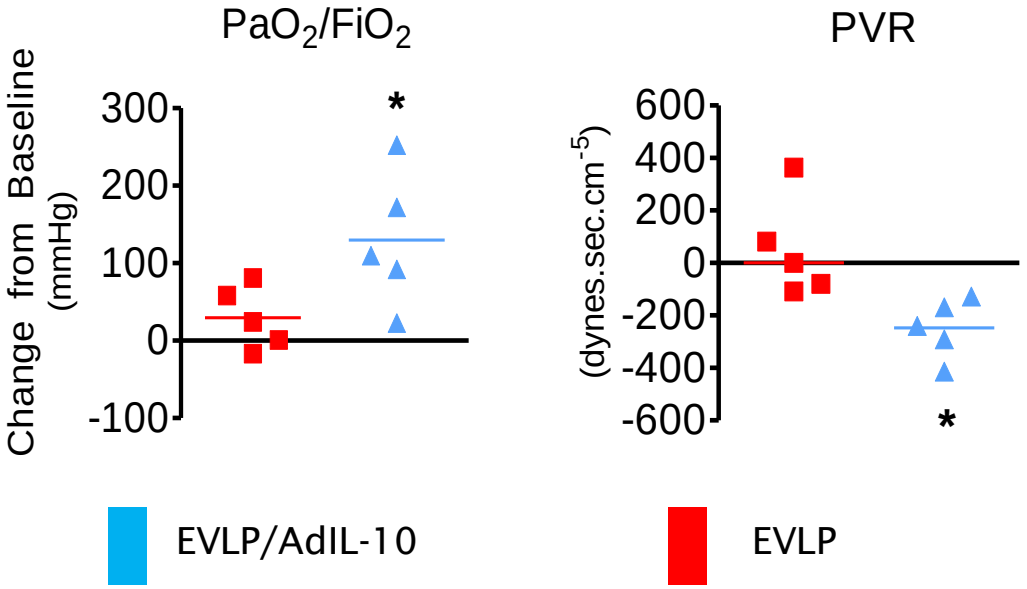
6. Expression of therapeutic mRNA and protein



Functional Repair of Human Donor Lungs by Ex Vivo IL-10 Gene Therapy

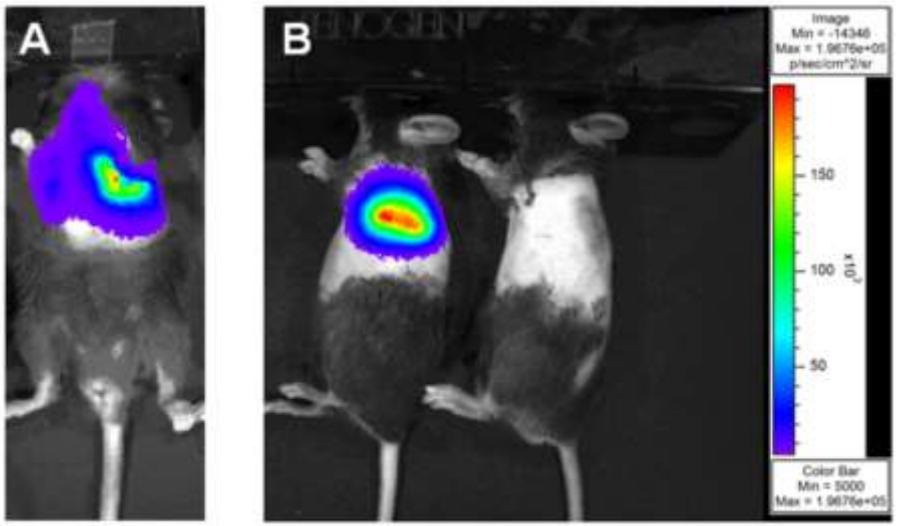
Delivery of IL-10 by EVLP Ad Gene Therapy to injured human donor lungs resulted in improved lung function

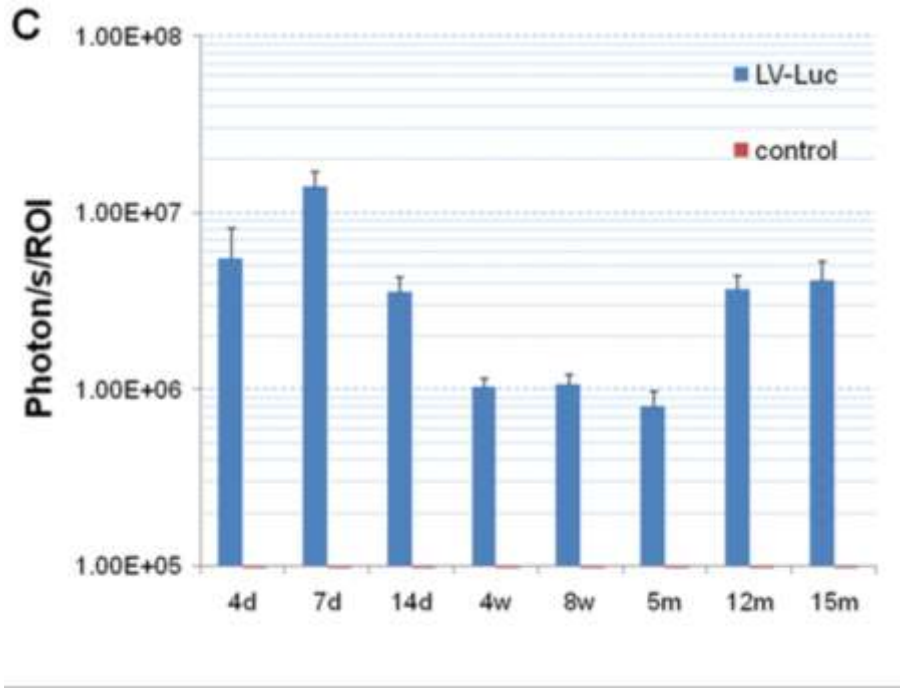




M Cypel, M Liu, M Rubacha, J C Yeung, S Hirayama, M Anraku, M Sato, J Medin, BL Davidson, M de Perrot, TK Waddell, A S Slutsky, S Keshavjee. *Sci Trans. Med* 1:4ra9; 2009.

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





Hirayama/ Keshavjee et al. *Human Gene Therapy* 2012.

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

Treatment Strategies

Perfusion

Gene Therapy

Drugs

Cell Therapy

Biological

Immuno-cloaking

Inhaled Gases

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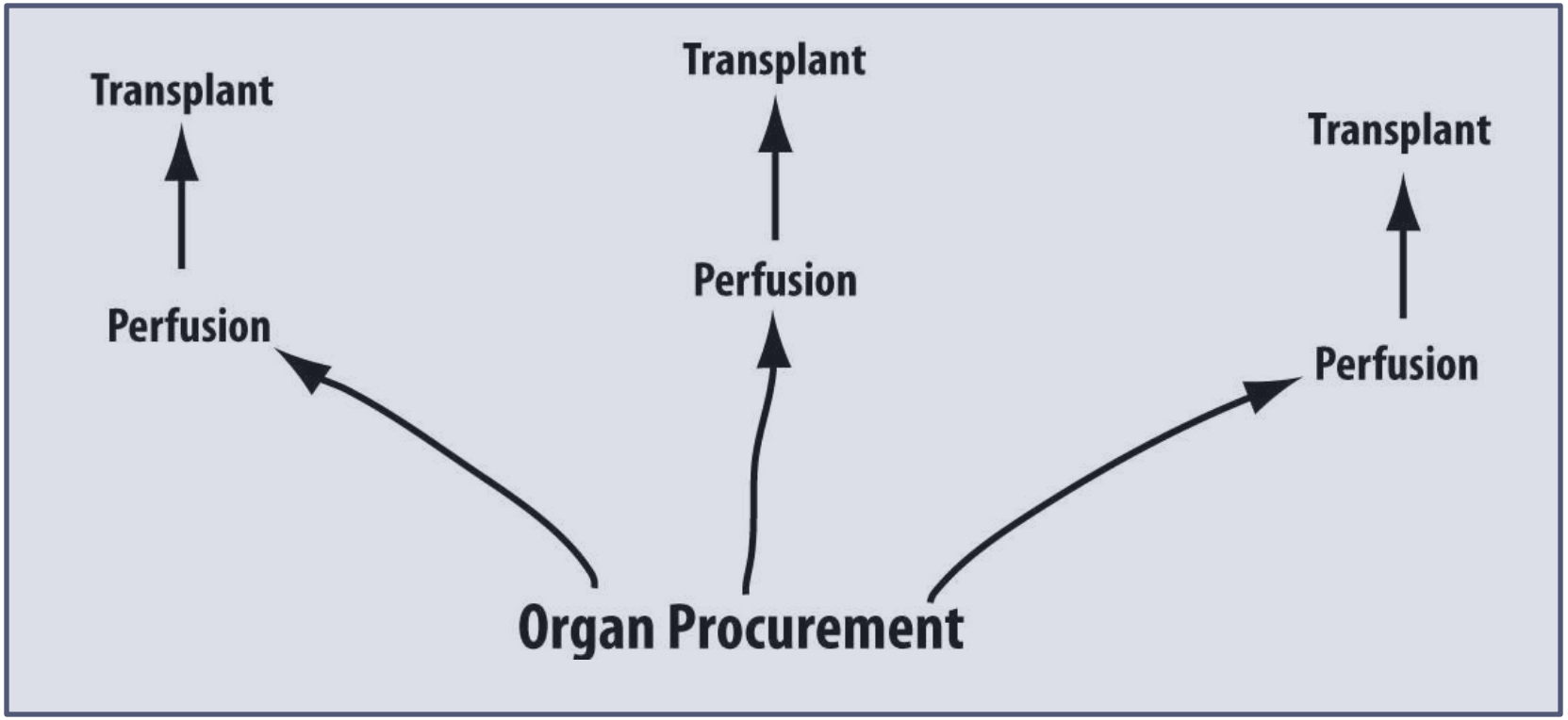
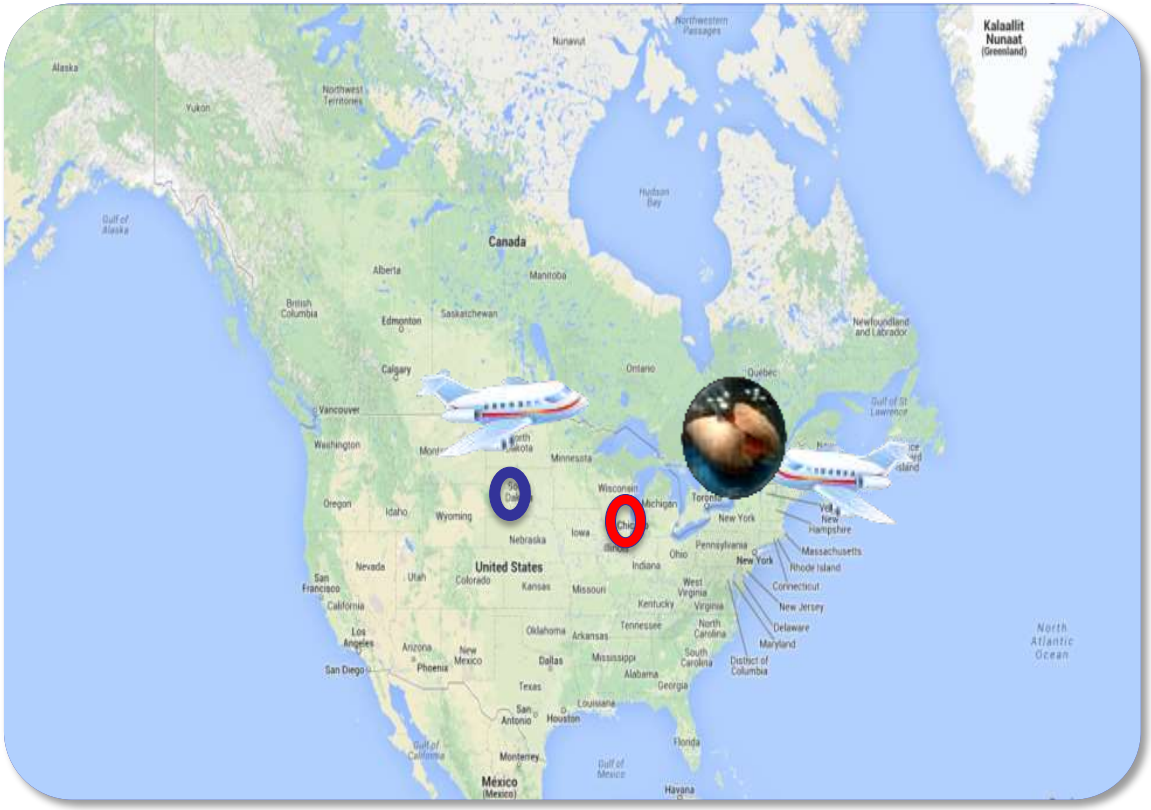
How Do We Translate the Knowledge and Scale Up Ex vivo Organ Repair Worldwide?

- Transplant Center - Centric Model



Organ Repair Centre
Toronto General Hospital April 2011



Wigfield CH, Cypel M, Yeung J, Waddell T, Alex C, Johnson C, Keshavjee S, Love RB. Successful emergent lung transplantation after remote ex vivo perfusion optimization and transportation of donor lungs. *Am J Transplant* 2012; 12(10):2838-44.

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Another World First…

American Journal of Transplantation 2012; 12: 2838–2844
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.04175.x

Case Report

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

C. H. Wigfield[a,*], M. Cypel[b], J. Yeung[b], T. Waddell[b], C. Alex[c], C. Johnson[d], S. Keshavjee[b] and R. B. Love[a]

Am J Transplant 2012

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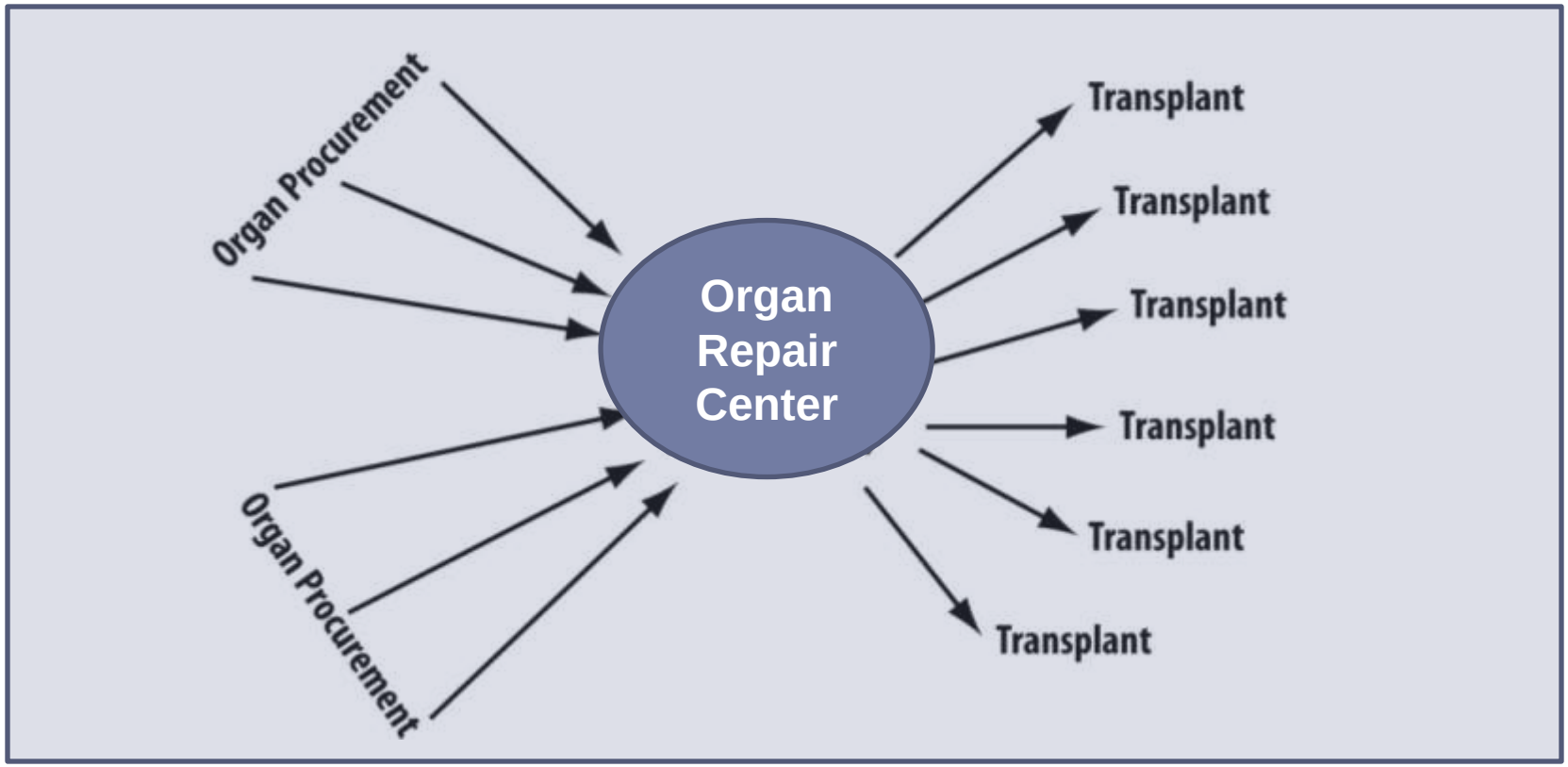
How Will We Apply and Scale Up Organ Repair Clinically?

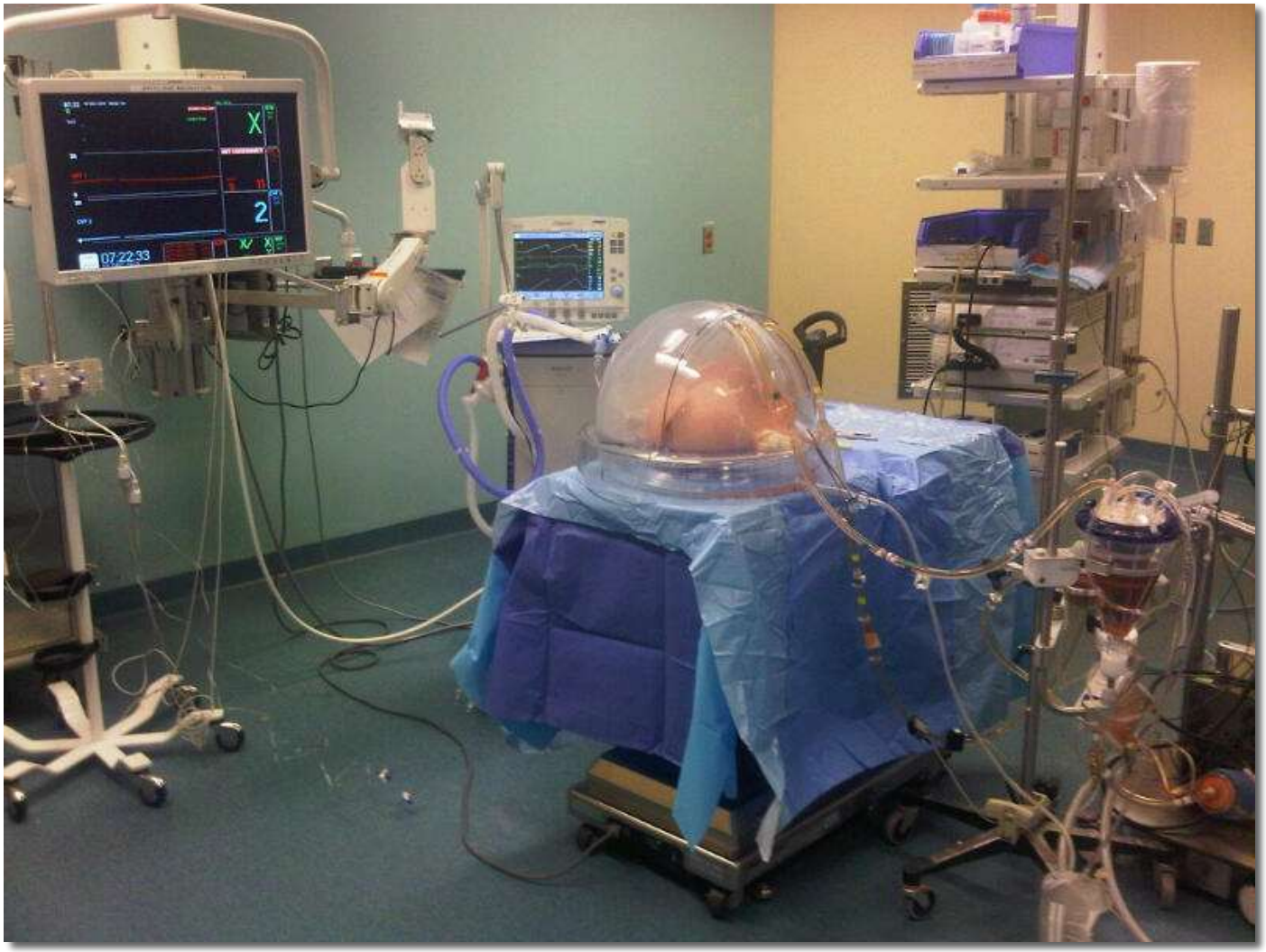
Organ Repair Hub Model



The "Organ Repair Center"

Lung

Heart



Liver

Kidney

The Future of Organ Transplantation
XOR

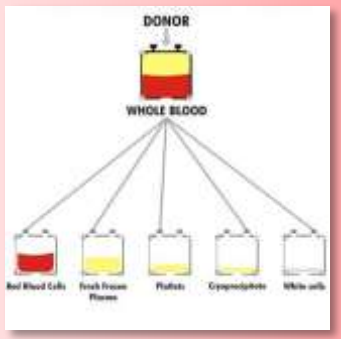
How do we put this all together?

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

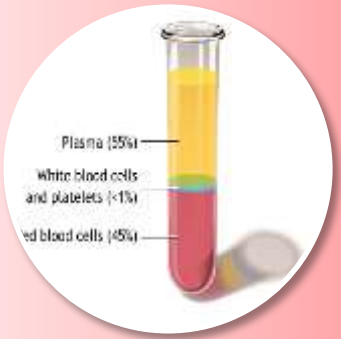
The History of Blood Transfusion

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

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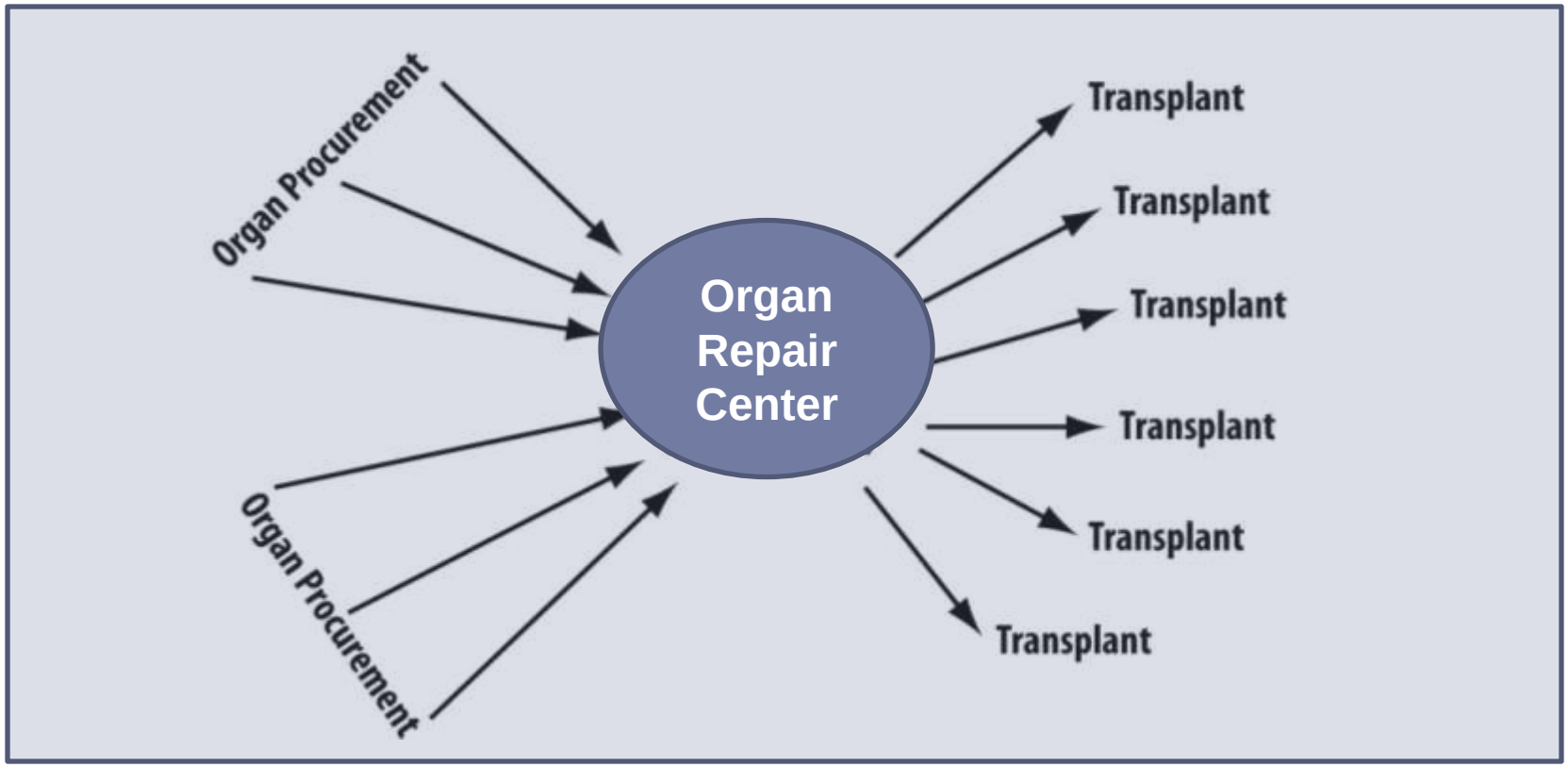
Can we apply these concepts to the management of donor organs for transplantation?

The Future State…

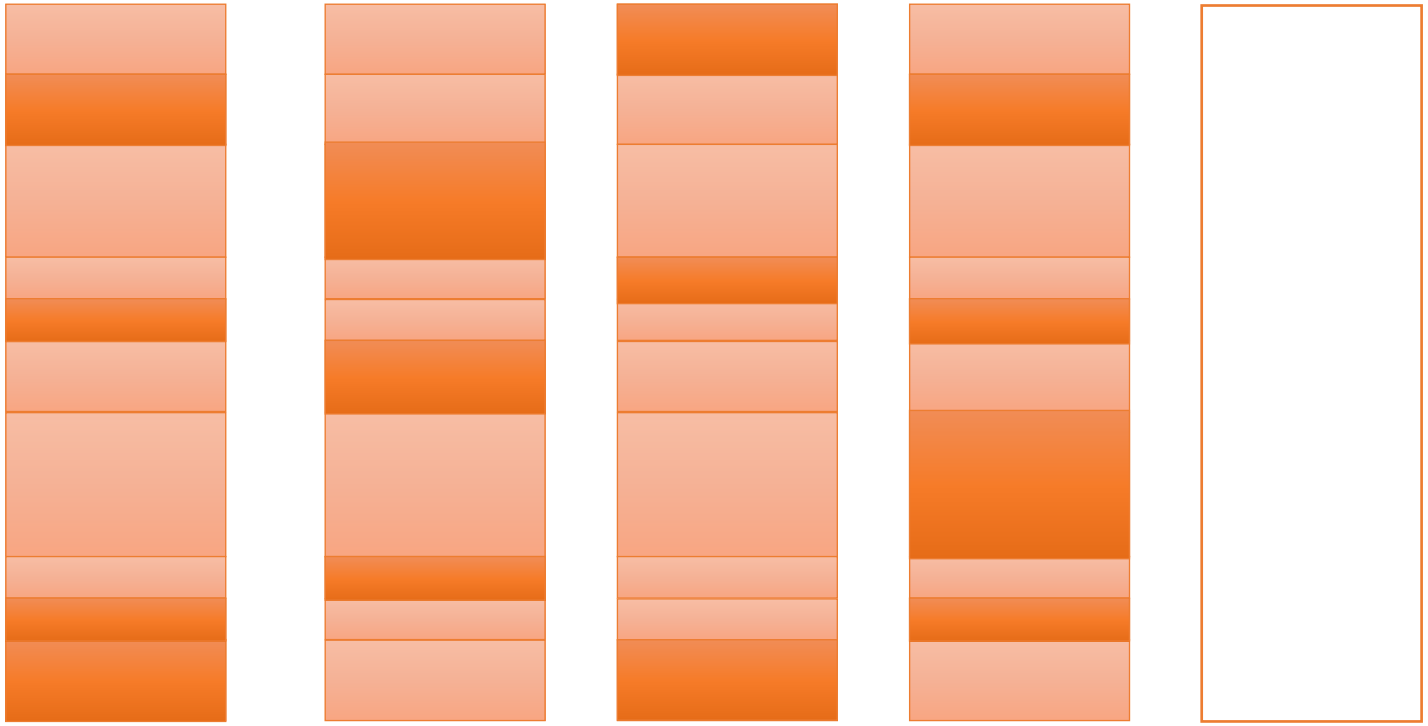
Organ Repair Hub Model



“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

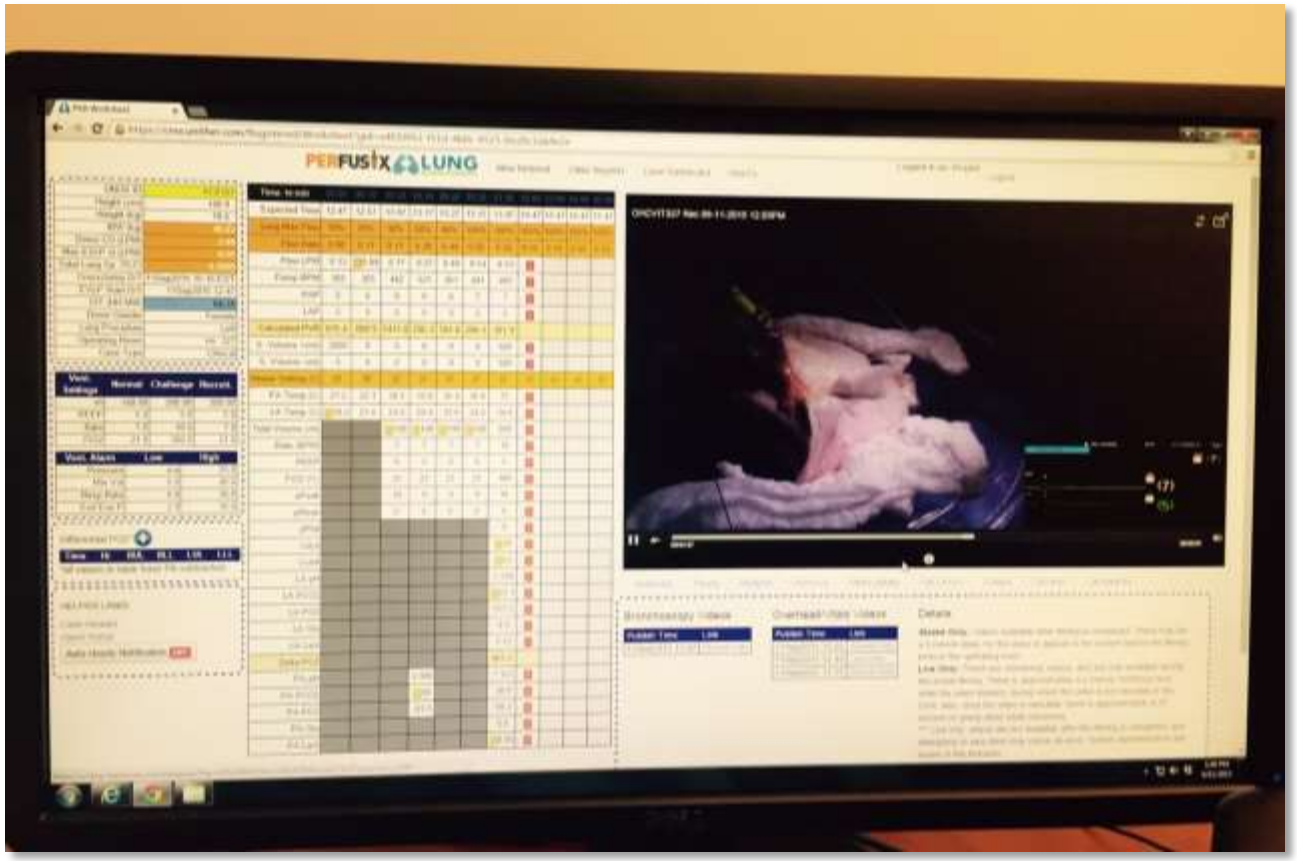
RT

Surgical

Other
Sub-Specialties

Certified Ex-Vivo
Lung Specialist

Perfusix – Lung Bioengineering
Lung Restoration Center
Remote Surgeon Data Interface



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PX2 (Jacksonvile Florida) and PX3 (Phoenix Arizona) - Perfusix, Lung Bioengineering, United Therapeutics and Mayo Clinic

Organ Repair Laboratories in North America (Lung Restoration Centers)

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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

Fails

Excellent

Current Practice

TRANSPLANT

No Transplant

Personalized Medicine for the Organ

DONOR LUNG

Clinical Assessment

Fails

EVLP

Functional Assessment

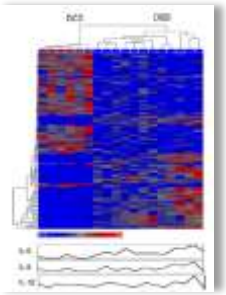
Fails

Suitable

Rapid Bioprofiling

Fails… or Could be Improved

Ex vivo Repair Strategies



Diagnostic Accuracy, Confirmation, Safety

Reassess

Fails

TRANSPLANT

No Transplant

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…

Doctors of Thoracic Surgery

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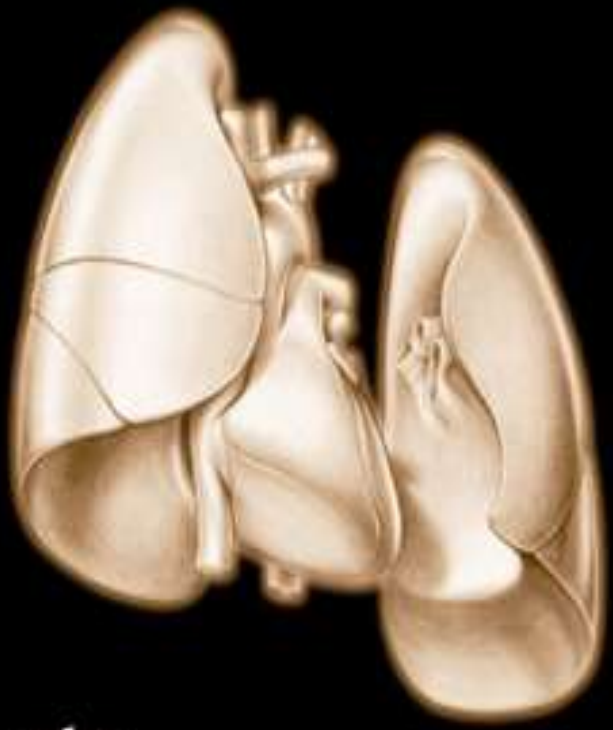

The Toronto Lung Transplant Program