Cross Circulation ECMO for Organ Recovery, Biohybrid Lung and New Devices

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No Disclosures
The Need

• **25 million** Americans suffer from end-stage lung disease
• **400,000** patients die every year
  • **2,692** added to transplant list
• **2,345** lung transplants in USA in 2016
• Lung transplantation is only definitive treatment
• Limited by shortage of transplantable donor lungs
• Average survival of approximately 5 years
The Need for Donor Organs

Only 1 in 5 donor lungs are usable for transplantation

- Trauma
- Pulmonary Contusion
- Infection
- Edema
- Mechanical ventilation / ICU Care

* Organ Procurement and Transplantation Network
Lung Transplant Waitlist and Donor Pool

Wait list mortality
- 10% per year
- Bridge to transplant

How do we expand the donor Pool?
Lung Transplant Waitlist and Donor Pool

Wait list mortality continues to rise
• 10% per year

How do we expand the donor Pool?

• Expanded Criteria Lungs
• Selective use of DCD Donors
• Ex-Vivo Lung Perfusion (EVLP)
• Bioengineered lungs
• Artificial lungs
• Xenotransplantation
State of the Art: *Ex Vivo* Perfusion

To recover *marginal quality* donor organs

- **Lung**
  - unacceptable
  - marginal
  - **OCS™**

**Limited time to intervene (6hr)**
Limitations of devices & lung bioengineering

Bioengineered lungs: fix bad lungs, make new lungs

Extracorporeal devices: improve marginal quality lungs

Organ complexity: (lack tools, methods)

Limited 6 hour support time: (too short for recovery)
The Clinical Goals inform our Research Objectives

Significantly *increase the number of donor organs* and *improve the durability and homeostasis of MCS support*
Lung Regeneration

Lung Stem Cells → Bioreactor → Lung Scaffold → Lung graft

Study diseases, drugs
Lung Engineering – Early Efforts

Decellularization of rat lungs

Repopulated with primary epithelial and endothelial lung cells that could participate in gas exchange upon transplantation

BUT

Lungs failed after only a few hours because of clots and leakage

Lung Anatomy

**Cell type**
- Epithelium → EPCAM
- Alveolar T I → Aquaporin 5
- Alveolar T II → Surfactant C
- Endothelium → von Willebrand F/CD31
- Fibroblast → Vimentin
- Myofibroblast → α-SMA
- Pericyte → NG2
- Immune cells

**ECM**
- Collagen IV
- Elastin
- Laminin
- Fibronectin

**Other components**
- Aquaporin 5
- von Willebrand F/CD31
- Vimentin
- α-SMA
- NG2

**Cell markers**
- EPCAM
- Connexin 43
- ZO-1
How to overcome the problems of decellularization?

- Decellularize rat lungs while keeping the vasculature alive
- Repopulate with stem cell-derived lung progenitors instead of primary cells
Hypothesis

The de-epithelialized matrix and ventilation of rat lungs ex vivo will allow engraftment and differentiation of pulmonary epithelial stem cells. If we were able to maintain structural integrity.

Goal – To engineer a functional rat lung capable of gas exchange.
Lung Engineering – Small Animal Models

Roller Pump
Membrane Oxygenator
Oxygen Source
ECMO

Heparin
Decell solution (CHAPS)

Left lung ventilation
Right lung decellularization
decellularization cell replacement
untreated
de-epithelialized
LUNG DISEASE

Functional vascularized lung grafts for lung bioengineering

N. Valerio Dorrello,¹,² Brandon A. Guenthart,²,³* John D. O’Neill,²* Jinho Kim,² Katherine Cunningham,² Ya-Wen Chen,⁴,⁵ Mauer Biscotti,³ Theresa Swayne,⁶ Holly M. Wobma,² Sarah X. L. Huang,⁴,⁵† Hans-Willem Snoeck,⁴,⁵,⁷,⁸ Matthew Bacchetta,³ Gordana Vunjak-Novakovic²,⁵‡
Vascular preservation, viability and function

Preservation of lung structure and ECM

Vaso-active Responsiveness
Cell delivery, attachment and viability in de-epithelialized lung

Improved compliance
Conclusions

• A mild decellularization approach on EVLP only via airway allows an efficient removal of lung epithelium (de-epithelialization)

• The system preserves bronchial and vascular architecture and viability

• It provides a favorable milieu for engraftment of lung epithelial cells as well as h-iPS derived lung progenitors
Lung Engineering – Large Animal Models

Donor Lung → EVLP

Ex-vivo Intervention

ECMO

In-situ Intervention
Lung Engineering – Imaging modalities

- Bronchoscopic delivery
- Thermal imaging
- Bronchoscopy

i. NIR
ii. MSC
iii. pleura
Advanced imaging guides therapeutic interventions

BullsEye Bronch™
Fiber Optic Bundle

2 mm

Autonomous Navigation
Airway

Delivered NIR Cells

Trans-pleural imaging

Original
Cell Tracker
Cell Count
Advanced imaging guides therapeutic interventions.
Extracorporeal lung theranostic toolkit

Thermography  Transpleural  Bronchoscopy

Fiber optics  Fluorescence  Live cell

Time-lapse  X-ray  Bioluminescence
Theoretical solution to the organ support barrier

Incorporate the functionality of multiple key organs

- Kidney
- Pancreas
- Liver
- Injured donor lung

Durable homeostatic physiologic milieu
**Cross-circulation:** envisioned clinical application

- heart/lung
- kidney
- intestine
- bioengineered grafts
- pancreas
- liver
- xenogeneic organ grafts
- limb salvage

- Recovery over days – weeks
- Transplantation

- Unacceptable for transplantation

Durable homeostatic physiologic milieu
Cross-circulation platform: organ recovery + research

- Heart/lung
- Kidney
- Liver
- Intestine
- Pancreas
- Bioengineered grafts
- Limb salvage
- Xenogeneic organ grafts

Recovery over days - weeks

Transplantation

Unacceptable for transplantation
Cross-circulation in a human-scale model (pig)
Recovery of injured lungs with cross-circulation
Lung Engineering – Cellular Analysis for *Extended* Organ Preservation

**Epithelial Integrity**
- Pan-Cytokeratin
- H&E

**Type II Cells**
- BODIPY-SPB
- DAPI Ac-LDL

**Mitochondrial Activity**
- OD
- Time (XC)
- p < 0.01

**Acetylated-LDL Uptake**
- CD 31

**Endothelial Integrity**
- CD 31

**Vasoresponse**
- epinephrine
- Pressure (mmHg)
Functional recovery of injured lungs using cross-circ.
Cross-circulation published in a Nature journal

Organ transplantation: Lung repair via cross-circulation

Leonidas Tapia & Harald C. Ott

Extracorporeal cross-circulation between lungs enables the extended support of recipient lungs and the recovery of injured lungs in a swine model.
Cross-circulation to recover lungs from an injury

Studies complete, manuscript in preparation
Lung recovery from an injury

1. procurement
2. lung cannulation
3. EVLP
4. recipient cannulation
5. Injured lungs on cross-circulation
Cross-circ enables interventions to recover injured lungs

1. Airway “lavage” (washing)  
2. Surfactant delivery  
3. Stem cell delivery
Lung recovery from an injury
Lung recovery from an injury
Cross-circulation recovers lungs from an injury.
Successful transplantation of recovered lungs (pig)

‘Potter’ (post-op transplant recipient)
Cross-circulation requires a complex set up.
Our ultimate goal is to salvage an organ (lung, liver) that was unacceptable for transplant, recover the organ with cross-circulation, and enable a life-saving transplantation.
Summary

• There is a great disparity between organ need and donor organ availability. **The Driver ➔ Innovation**

• Current technology, e.g. Ex vivo systems, offers marginal impact on donor shortage because of its physiologic limitations

• Functionalized lung graft development offers a mechanism for bioengineering the epithelium-airway

• The cross-circulation platform provides a durable homeostatic environment
  • Extended recovery periods for rejected lungs and other organs
  • Support device to conduct long-term recellularization studies and organ modification
Biohybrid lungs: Why we like the idea

• Endothelialized artificial scaffolds or oxygenators

• Potential durable support

• Reduced need for anticoagulation
  • Reduced risk of thrombosis & bleeding

• Potential reduction in inflammatory cascade caused by exposure to artificial surfaces

• Holy grail of destination therapy?
HUVEC – umbilical origin
Membrane surface: nonporous fluorocarbon (lumox®)
Endothelium culture medium
Research Article
Towards a Biohybrid Lung: Endothelial Cells Promote Oxygen Transfer through Gas Permeable Membranes

2017

Sarah Menzel,1,2 Nicole Finocchiaro,1,2 Christine Donay,1,2 Anja Lena Thiebes,1,2,3 Felix Hesselmann,4 Jutta Arens,4 Suzana Djeljadini,5 Matthias Wessling,5 Thomas Schmitz-Rode,6 Stefan Jockenhoevel,1,2 and Christian Gabriel Cornelissen1,2,7

Table 2: Measuring points as well as their characteristic parameters for gas transfer tests.

<table>
<thead>
<tr>
<th>Measuring point (MP)</th>
<th>Flow rate V (ml.min⁻¹)</th>
<th>Residence time θ (s)</th>
<th>Wall shear stress τw (Pa)</th>
<th>Time of sampling (h)</th>
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<tr>
<td>1</td>
<td>0.4</td>
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<td>4</td>
<td>1.6</td>
<td>22</td>
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</table>

- Shear stress of 0.15 Pa
- Oxygen transfer
  - Better with Endo + Membrane
  - Improved with increased flow (non-linear within the range)
Endothelialized *porous* vascular grafts failed at 15 dyne/cm².

Oxygenators tend to generate >> Shear force.
Developing a biohybrid lung – sufficient endothelialization of poly-4-methly-1-pentene gas exchange hollow-fiber membranes

Bettina Wiegmann\textsuperscript{a,b,c,d,*}, Heide von Seggern\textsuperscript{e}, Klaus Höffler\textsuperscript{a}, Sotirios Korossis\textsuperscript{b}, Daniele Dipresa\textsuperscript{b}, Michael Pflaum\textsuperscript{b,d}, Sabrina Schmeckebier\textsuperscript{b,d}, Jörg Seume\textsuperscript{e}, Axel Haverich\textsuperscript{a,b,c,d}

Endothelialization and characterization of titanium dioxide-coated gas-exchange membranes for application in the bioartificial lung

Michael Pflaum\textsuperscript{a,b,*}, Marina Kühn-Kauffeldt\textsuperscript{e,1}, Sabrina Schmeckebier\textsuperscript{a,b}, Daniele Dipresa\textsuperscript{a,b}, Kanchan Chauhan\textsuperscript{a,b}, Bettina Wiegmann\textsuperscript{a,b,d}, Rolf J. Haug\textsuperscript{f}, Jochen Schein\textsuperscript{e}, Axel Haverich\textsuperscript{a,b,c,d}, Sotirios Korossis\textsuperscript{a,b,c}
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Fig. 1. Schematic illustrations of the (A) triggerless pulsed vacuum cathodic arc plasma deposition technique, and (B) gas-exchange test chamber. E. cells seeded and incubated
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Shear stress protocol:
Primed under 0.5 dyne/cm² for 1 hr
“physiological” stress of 30 dynes/cm² for 24 hr

Oxygen Transfer Rate

22%
Biohybrid lungs: The promise & the reality

The Promise

• Surface Endothelialization
  • Hemocompatibility
  • Functional, confluent, self-repairing

• Reduce or eliminate anticoagulation

• Durability
  • Destination therapy

The Reality

• Cell source
  • Human umbilical cord blood (HUVEC)
  • Immunologic privilege?
  • Patient derived cells
    • Extreme personalized medicine

• Durability of cell-surface contact
  • Can an artificial surface provide cell adhesion?
    • Cell matrix matters ⇐

• In vivo biohybrid lung scale up
  • Flow chamber design optimized
    • Lower flow resistance
    • Homogenous flow
  • Surface area requirements for endothelial coverage

• Oxygen transfer
  • TiO₂ coating impact; any surface layer
# Our Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
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<tbody>
<tr>
<td>Gordana Vunjak-Novakovic, PhD</td>
<td>University Professor, Biomedical Engineering</td>
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<td>John O’Neill, PhD</td>
<td>Biomedical Engineering</td>
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<tr>
<td>Ahmed Hozain, MD</td>
<td>General Surgery</td>
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<td>Scott Chicotka, MD</td>
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<td>Meghan Pinezich, BSE</td>
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