Developing an Off-the-Shelf Living Tissue Supply

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Organ Preservation Alliance
organpreservationalliance.org
Direct current, electric battery
(developed in 1800)

Alternating current
(developed in 1832)
CRYOPRESERVATION

- Tissue Engineering
- Trauma Care
- Basic Research
- Cancer Care
- Limb, Hand And Face Transplantation
- Drug Discovery
- Emergency Preparedness
- Reconstructive Surgery
- Organ Transplantation
CRYOPRESERVATION

Organ Transplantation

- Tissue Engineering
- Reconstructive Surgery
- Drug Discovery
- Emergency Preparedness
- Limb, Hand and Face Transplantation
- Cancer Care
- Trauma Care
- Basic Research
Need more organs

- U.S. transplants per year: 31,000
- U.S. waiting list: 122,000
- U.S. deaths per year from organ impairment: 900,000

Need better organs

- % of Organs Surviving over Years after Transplant for Heart, Liver, Kidney, Pancreas, Intestine, Lung

Source: SRTR, 2015
Revolutionary organ procurement capability:

**The Gift of Time**

- Higher Utilization
- Better Matches
- Less Ischemic Injury → Less Rejection
- Immune Tolerance
- Lower Costs of Transport
- Elective Surgery and Allocation
- Increase Placement for Research
“Organ cryopreservation would be perhaps the most important breakthrough in transplantation in the last 50 years.”

- Dr. David Nelson
Chief of Heart Transplantation, Baptist Integris Medical Center
Highest performing heart transplant program in the U.S., 2002 and 2012
Table 2. Preservation enables key transplant capabilities.

| Function | Prior to Transplant | After Preservation
|----------|---------------------|---------------------|
| Organ function | Poor due to ischemia-reperfusion injury | Good due to preservation
| Organ size | Shrunken due to ischemia-reperfusion injury | Normal due to preservation
| Organ perfusion | Impaired due to ischemia-reperfusion injury | Improved due to preservation
| Organ viability | Low due to ischemia-reperfusion injury | High due to preservation
| Organ infection | Increased due to ischemia-reperfusion injury | Decreased due to preservation
| Organ malignancy | Increased due to ischemia-reperfusion injury | Decreased due to preservation

Complex Tissue Preservation: Overcoming a Common Challenge

The use of transplantation (discussed below) that preserves and impairs restores and extends the life of the organ.

Examples of 'proof-of-concept' discoveries

- Reduced hyperacute rejection
- Improved organ function
- Reduced tissue loss
- Improved survival
- Reduced complications
- Improved patient outcomes
- Reduced transplant wait times
- Reduced healthcare costs
- Reduced hospital stays
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Many Missions. . .

A Common Challenge
Beta Roadmap Report

SOLVING ORGAN SHORTAGE THROUGH ORGAN BANKING AND BIOENGINEERING

The Grand Challenges of Organ Banking: Proceedings from the first global summit on complex tissue cryopreservation

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Second half of grants were greenlit before getting Phase 1 results from the first half.

“The strength and number of grant applications were unprecedented.”

-Lt. Col. Luis Alvarez, PhD
Program officer for the grants
“What started as a long-shot effort to preserve a rabbit kidney is now a collaborative, government funded endeavor.”
WHITE HOUSE HIGHLIGHTS AST'S NEW INITIATIVE WITH ORGAN PRESERVATION ALLIANCE

Thursday, December 22, 2016
FOR IMMEDIATE RELEASE
A modern day Apollo program

Virtually all organ & tissue systems

Massive Design Space

Divisible into sub-challenges
1. Control ice formation
2. Limit cryoprotectant toxicity
3. Limit thermomechanical stress
4. Contain and repair ischemic injury
5. Prevent excessive chilling injury
6. Assure acceptable revival and repair

Multiple technology areas required

Imaging
High throughput screening
Programmed hypometabolism
Gene editing
Supercooling
Ex vivo perfusion
Vitrification
Bioinformatics
Nanotechnology
Computational chemistry
Viable banking:

A scale-up challenge

- Whole organs
- Vascularized composite tissues
- Research animals
- Reproductive organs
- Transplant tissues
- Research tissues
- Zebrafish
- Arms Hands Digits
- Hearts Kidneys Livers
- Lungs Pancreata Intestines
- Ovaries Testes
- Skin Blood vessels Cardiac Patches Pancreatic islets
- Ovarian tissue Testicular tissue Cartilage Nerves
- Heart slices Liver slices Brain tissue Skin
- Kidney tissue Brain organoids Heart on a chip Liver on a chip
Proofs of concept: successful cryopreservation of living tissues and organs...

- Human ovarian tissue strips (1999)
- Human fingers (2009)
- Rabbit kidney (2009)
- Human cartilage (2013)
- Sheep ovaries (2014)
- Rat livers (2014)
- Rat limbs (2017)
- Rat hearts (2018)
- Human livers (2019)
“. . .high chondrocyte viability for up to two years (~94% avg.). . ."
Rubinsky Lab, UC Berkeley:
Rubinsky Lab, UC Berkeley:

Rubinsky Lab and Sylvatica Biotech:

10% cryoprotectant:

30% cryoprotectant:

Uygun Lab, Massachusetts General Hospital:

HP (4°C) — 3hr SNMP (21°C) — 1hr Preconditioning (4°C)

20hr Supercooling (-4°C) — 3hr SNMP (21°C)

3-4X storage!

A Human Liver Can Be Cooled to -4 Degrees Celsius and Survive

SARAH ZHANG  SEP 9, 2019

Supercooling preserves donor livers for more than a day
647,000 U.S. deaths from heart failure per year
3,400 U.S. heart transplants per year
The other 199 out of 200 patients:

~1 year average survival on today’s drug regimen
Human Organotypic Cultured Cardiac Slices: New Platform For High Throughput Preclinical Human Trials

C. Kang1,2, Y. Qiao1,2, G. Li3, K. Baechle1, P. Camelliti1, S. Rentschler1 & I. R. Efimov1,2,4,5

0 Hours  48 Hours  72 Hours  96 Hours
Neurology’s Silent Killer: Drug-Resistant Epilepsy

Disparities in Surgery Among Patients with Intractable Epilepsy in a Universal Health System.

OBJECTIVE: To assess the use of epilepsy surgery in patients with medically intractable epilepsy in a publicly funded universal health care system. METHODS: We performed a population-based retrospective cohort study using linked health care databases for Ontario, Canada, between 2001 and 2010. We identified all patients with medically intractable epilepsy, defined as those with seizures that did not respond to at least 2 adequate trials of seizure medications. We assessed the proportion of patients who had epilepsy surgery within the following 2 years. We further identified the characteristics associated with epilepsy surgery. RESULTS: A total of 10,661 patients were identified with medically intractable epilepsy (mean age 47 years, 51% male); most (74%) did not have other comorbidities. Within 2 years of being defined as medically intractable, only 124 patients (1.2%) underwent epilepsy surgery. Death occurred in 12% of those with medically intractable epilepsy. Those who underwent the procedure were younger and had fewer comorbidities compared to those who did not. CONCLUSION: In our setting of publicly funded universal health care, more than 10% of patients died within 2 years of developing medically intractable epilepsy. Epilepsy surgery may be an effective treatment for some patients; however, fewer than 2% of patients who may have benefited from epilepsy surgery received it.

What Your Doctor Won’t Tell You About Epilepsy: It Can Kill You

By Kurt Eichenwald

Of the ways epilepsy can kill, SUDEP (sudden unexpected death in epilepsy) is believed to be the most common. Getty Images
Clinical Neuroscience

An organotypic brain slice preparation from adult patients with temporal lobe epilepsy

Emmanuel Eugène a,b,c,d,*, François Cluzeaud c, Carmen Cifuentes-Díaz b,c,d, Desdemona Fricker a, Caroline Le Duigou a, Stéphane Clemenceau a, Michel Baulac a, Jean-Christophe Poncer b,c,d, Richard Miles a,**
How pieces of live human brain are helping scientists map nerve cells

An audacious project aims to figure out how humans are different from other creatures

By Laura Sanders
AUGUST 7, 2019 AT 6:00 AM
Employing “living biobanks” to advance biomedical research

March 21, 2019

Co-Chairs

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The Promise of Organ and Tissue Preservation to Transform Medicine


Abstract

The ability to repair organs and tissues on demand could save or improve millions of lives each year and could extend human life expectancy. Organ and tissue preservation relies on cryopreservation, mechanical stabilization, and other techniques that have been developed for decades. However, recent advances in cryopreservation and mechanical stabilization have allowed researchers to develop new techniques that could improve the survival of damaged organs and tissues. These techniques have the potential to revolutionize the medical field and could lead to the development of new treatments for a variety of diseases.

Introduction

The promise of organ and tissue preservation to transform medicine lies in the ability to repair damaged organs and tissues on demand. This is achieved through cryopreservation, mechanical stabilization, and other techniques that have been developed for decades. However, recent advances in cryopreservation and mechanical stabilization have allowed researchers to develop new techniques that could improve the survival of damaged organs and tissues. These techniques have the potential to revolutionize the medical field and could lead to the development of new treatments for a variety of diseases.

Table 1: Preservation enables key transplant expediency.

| Organ Type | Function | Prior to Transplant | After Transplant
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<tbody>
<tr>
<td>Kidney</td>
<td>Glomerular filtration</td>
<td>Reduced function</td>
<td>Normal function</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatic metabolism</td>
<td>Reduced function</td>
<td>Normal function</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiac output</td>
<td>Reduced function</td>
<td>Normal function</td>
</tr>
</tbody>
</table>

In addition, advances in cryopreservation and mechanical stabilization have allowed researchers to develop new techniques that could improve the survival of damaged organs and tissues. These techniques have the potential to revolutionize the medical field and could lead to the development of new treatments for a variety of diseases.

Complex Tissue Preservation: Overcoming a Common Challenge

The use of transplants (discussed below) that possess a large number of cells provides a unique opportunity for the development of a new field of study: tissue engineering. This requires the development of new materials and methods that can support the growth and function of living tissues. The development of new materials and methods that can support the growth and function of living tissues is a critical step in the development of tissue engineering.

Examples of “proof of principle” discoveries include:

1. Reduced heart failure in animals using biomimetic scaffolds.
2. Improved wound healing in diabetic patients using cell-based therapies.
3. Enhanced bone regeneration using chondrocyte-seeded scaffolds.
4. Improved liver function in rats using hepatic progenitor cells.

These examples demonstrate the potential of tissue engineering to transform medicine and provide hope for the future of organ and tissue transplantation.

Conclusion

The promise of organ and tissue preservation to transform medicine lies in the ability to repair damaged organs and tissues on demand. This is achieved through cryopreservation, mechanical stabilization, and other techniques that have been developed for decades. However, recent advances in cryopreservation and mechanical stabilization have allowed researchers to develop new techniques that could improve the survival of damaged organs and tissues. These techniques have the potential to revolutionize the medical field and could lead to the development of new treatments for a variety of diseases.

References


Acknowledgments

This work was supported by grants from the National Institutes of Health (R01EB014810, R01GM099281) and the California Institute of Technology.

Additional Information

Interactions between the liver, gut, and gut flora are critical for health and disease. A new study published in Nature Biotechnology has identified a novel mechanism that regulates the gut microbiota, which could lead to new treatments for diseases such as obesity and diabetes.

The study, conducted by researchers at the University of California, San Diego, used a combination of genetic and chemical approaches to identify a critical regulator of gut microbiota composition. The researchers found that a protein called Lkb1, which is expressed in the gut, plays a key role in maintaining the balance of the gut microbiota.

The results of this study have important implications for the treatment of diseases caused by imbalances in the gut microbiota. For example, the findings could be used to develop new treatments for obesity, diabetes, and other related conditions. Additionally, the study highlights the importance of understanding the complex interactions between the gut and the gut microbiota, which may have implications for a wide range of other diseases.

The study was supported by grants from the National Institutes of Health (R01EB014810, R01GM099281) and the California Institute of Technology.