

# ***New Opportunities Through Innovations***

*Jacques Pirenne, Transplant Surgeon, Leuven*

## **Organ Shortage**

**Xenotransplants?**

**Artificial Organs?**

**Maximize Deceased Donor Pool**

**New Preservation Techniques**

**Maximize Living Donor Pool**

*5th Journalist Workshop  
Organ Donation &  
Transplantation 26 /11/ 2014*



## **Dependence upon Anti-Rejection Drugs**

**Chronic Graft Loss: Mechanisms**

**Toxicity: Minimize & Avoid Anti-Rejection Drugs**

## **New Transplants**

**Regeneration & Organ Bioengineering : “Holey Grail”**

# Xenotransplants?

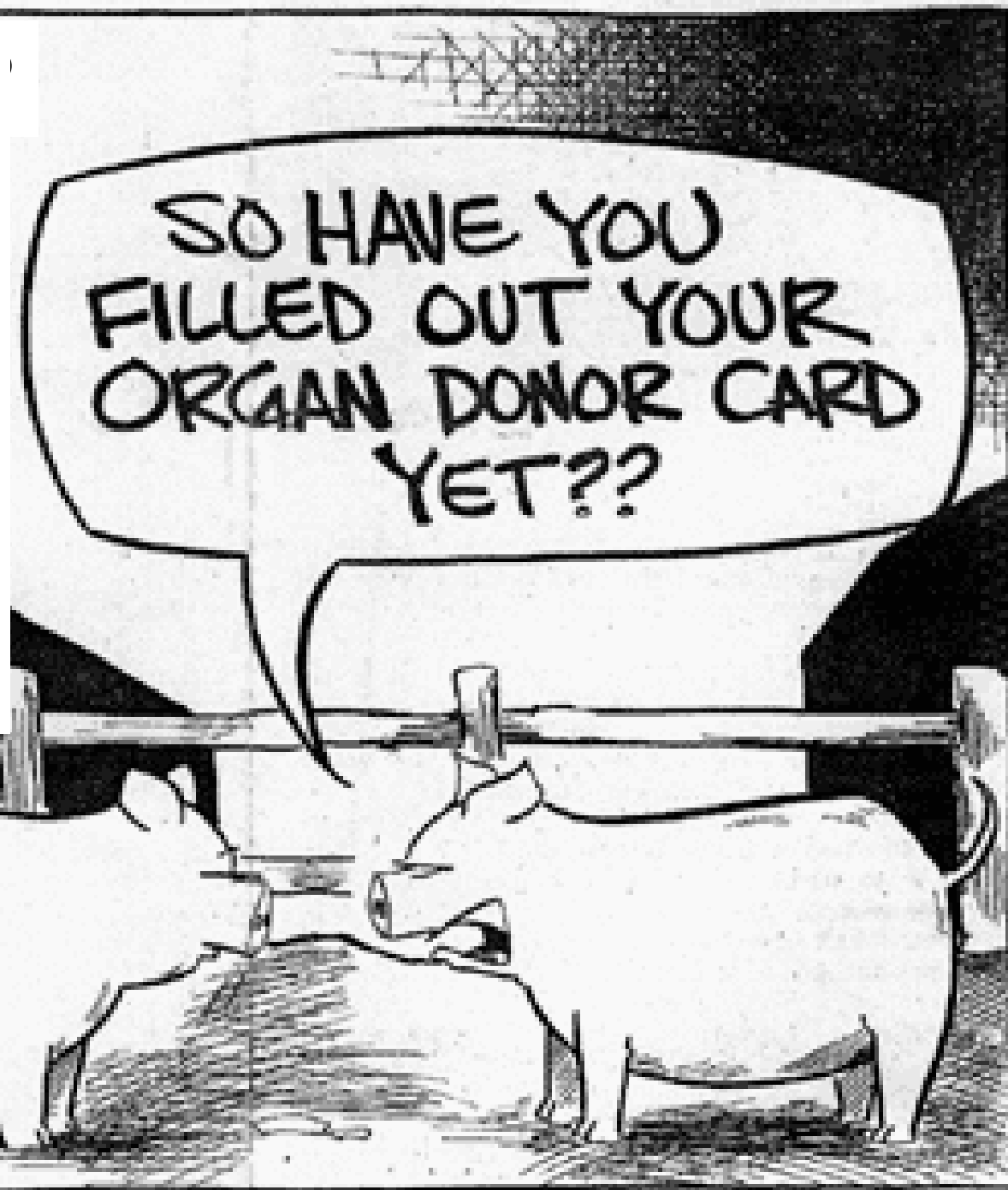


- Rejection +++



Genetically modified pigs

- Infection/Xenosis
- Physiological limits



# Artificial Organs = Bridge to Tx

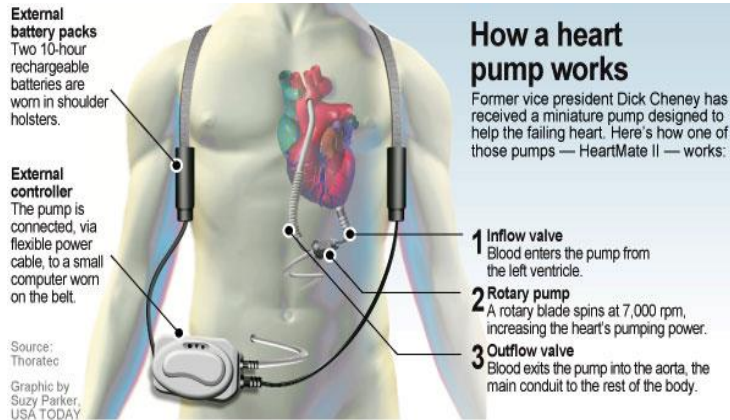


## Kidney Dialysis

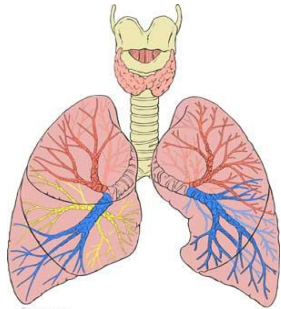
## Ventricular Assistance Device



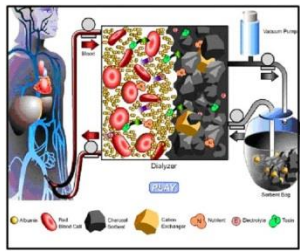
## Fully Implantable Device



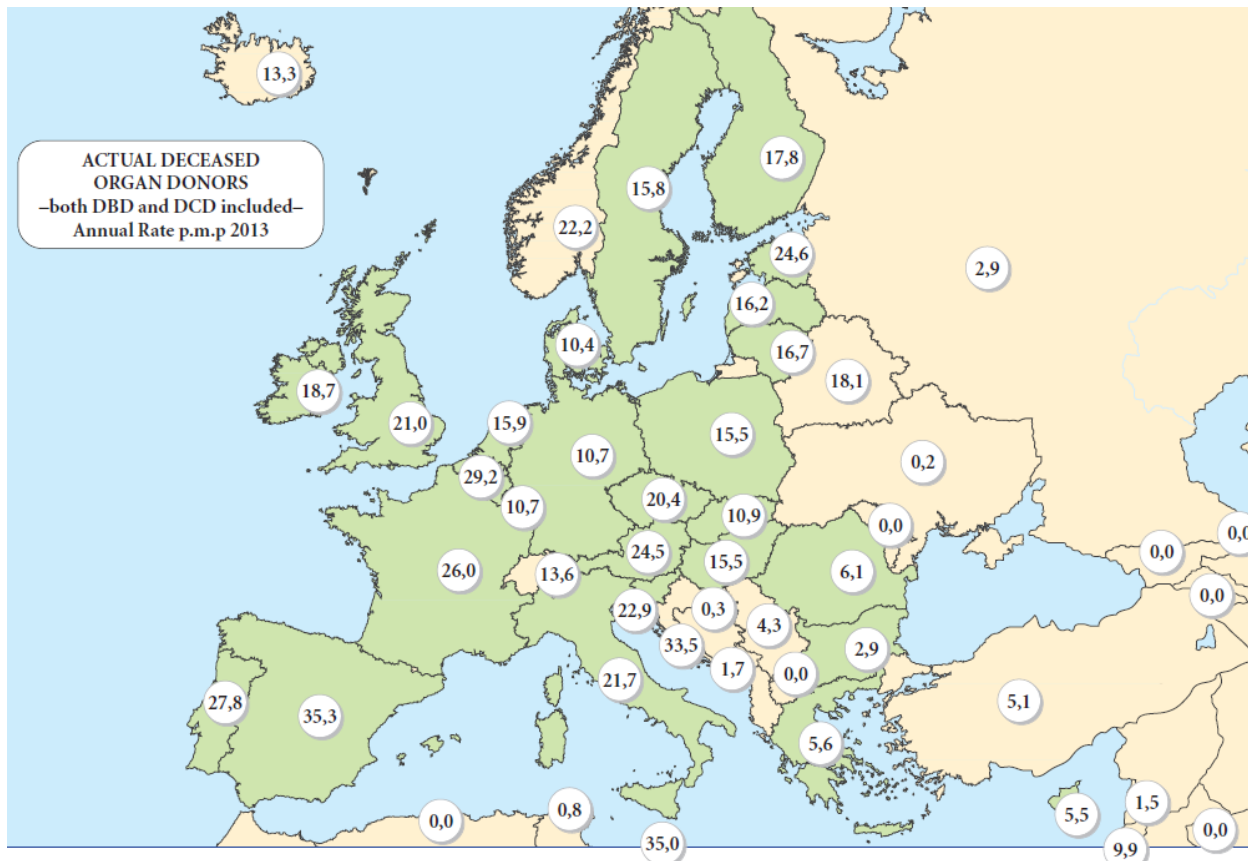
## Lung: Extracorporeal Membrane Oxygenation



## Liver "Dialysis"



# Maximizing Deceased Donor Pool



**Public Awareness**

**Legislation**

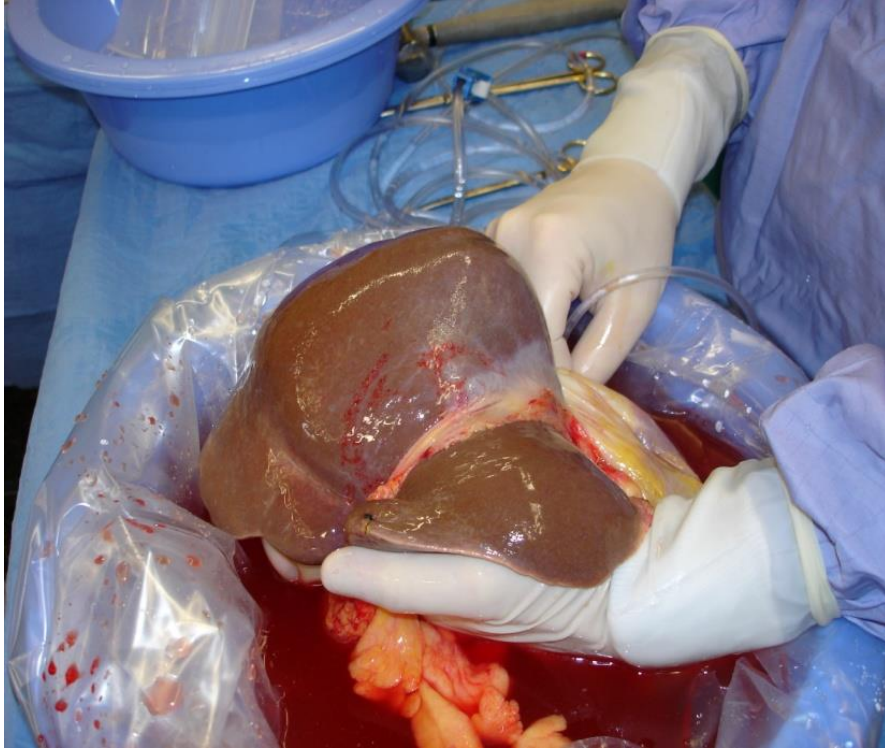
## **Detection**

- *Training (para) medical staff*
- *Optimize resources*



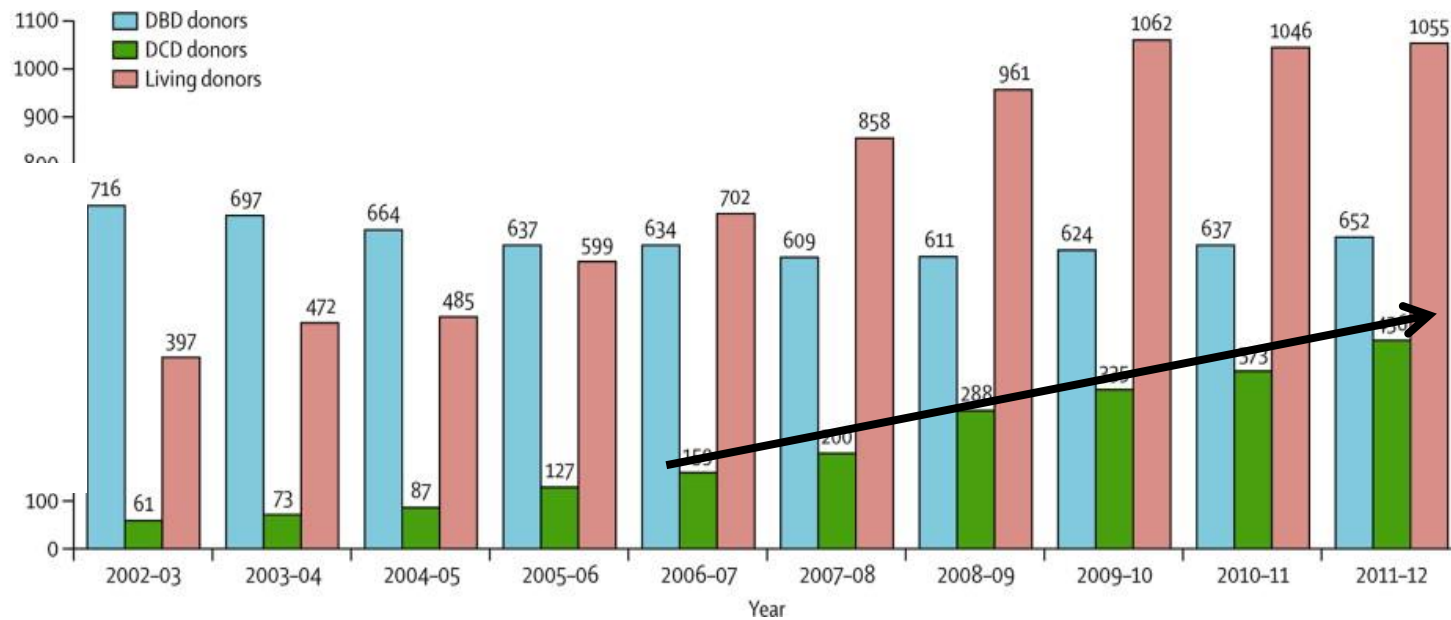
# Extension of Donor criteria

82 yo donor liver



Donation After Circulatory Death (DCD)

After euthanasia



# New Era in Preservation

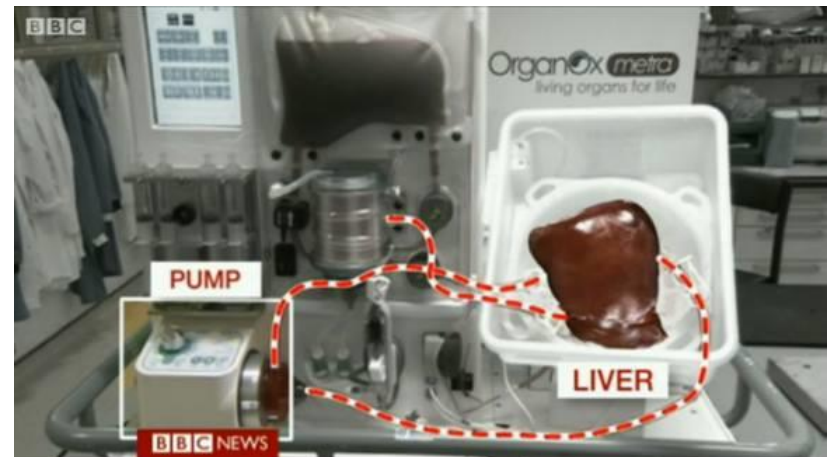
Simple cold storage



Cold perfusion



Warm Oxygenated Perfusion



# Warm Oxygenated Perfusion

= Keeping organs “alive” outside the body

- Better function posttransplant

- Evaluation of Viability

- Repair (non-Tx organs can be Tx)

- Longer Preservation (surgery at day time 😊)

- Modulation *against rejection, inflammation, infection*

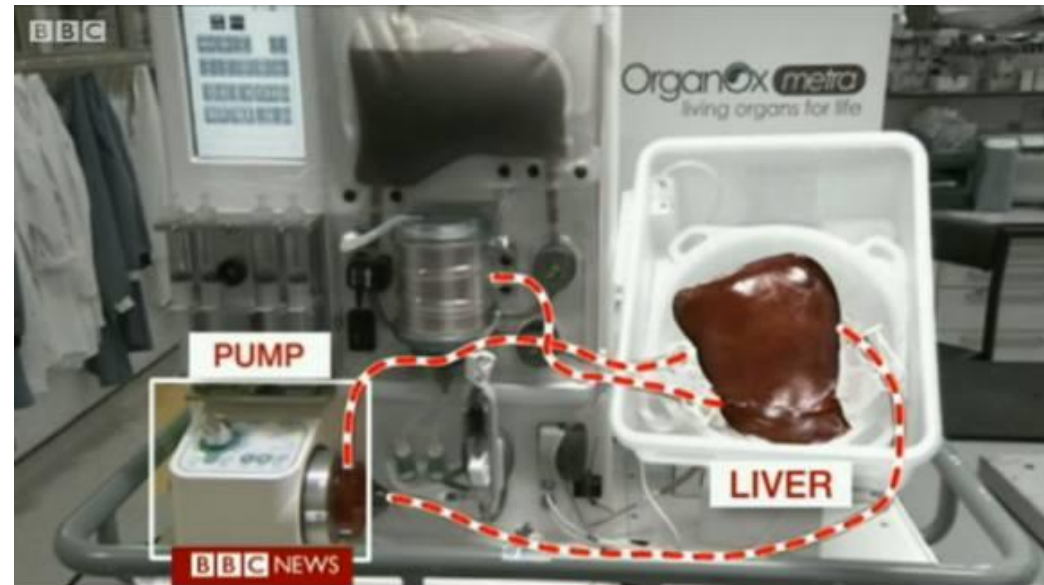
*\*Via Drugs, trophic factors, viral vectors, siMRNA, cells*





## Consortium on organ preservation in Europe

- Technology for organ reconditioning and preservation
- Kidney + Liver
- Coordinator: Rutger Ploeg, Univ Oxford
- ESOT link
- EU contribution: €6 million
- Four clinical trials
- [www.cope-eu.org](http://www.cope-eu.org)



- 20 livers successfully transplanted after warm preservation (Friend et al)
- Randomized Controlled Trial Started



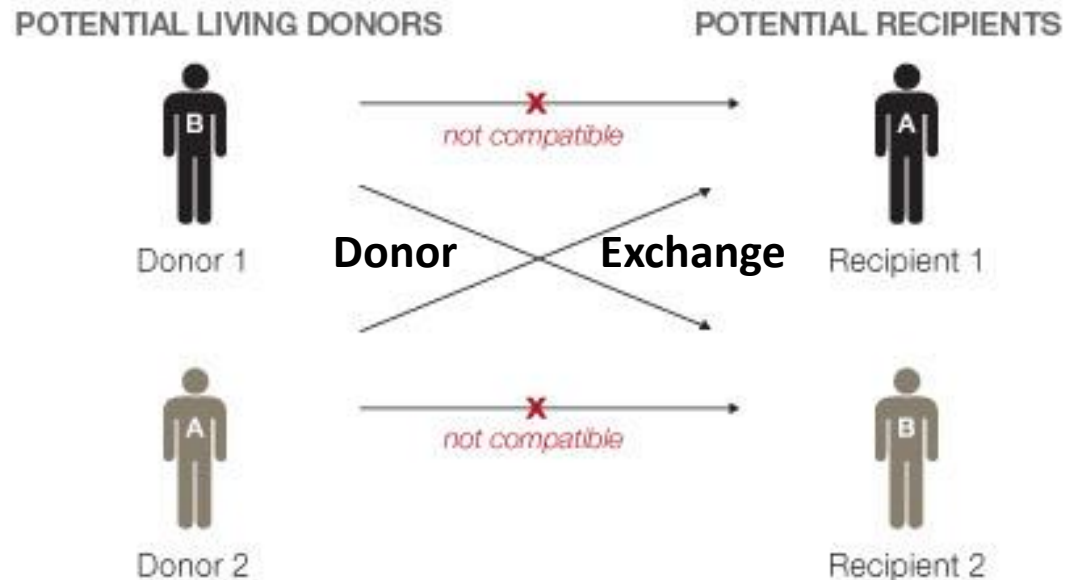
**First Successful  
Kidney Tx 1953**

# Maximizing Living Donor pool

**USA, Scandinavia, Holland: ~40-50%**  
**Belgium, France: ~5-10%**

**Information without coercion**

## ABO incompatible Tx



## Altruistic Donors

- *Give*
- *Anonymously*
- *To unknown recipient*
- *With no counterpart*

*Parabole of the Good Samaritan*  
*Stained glass window*  
*St Eutrope, Clermont-Ferrand, France*



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## **Dependence upon Anti-Rejection Drugs**

**Chronic Graft Loss: Mechanisms**

**Toxicity: Minimize & Avoid Anti-Rejection Drugs**

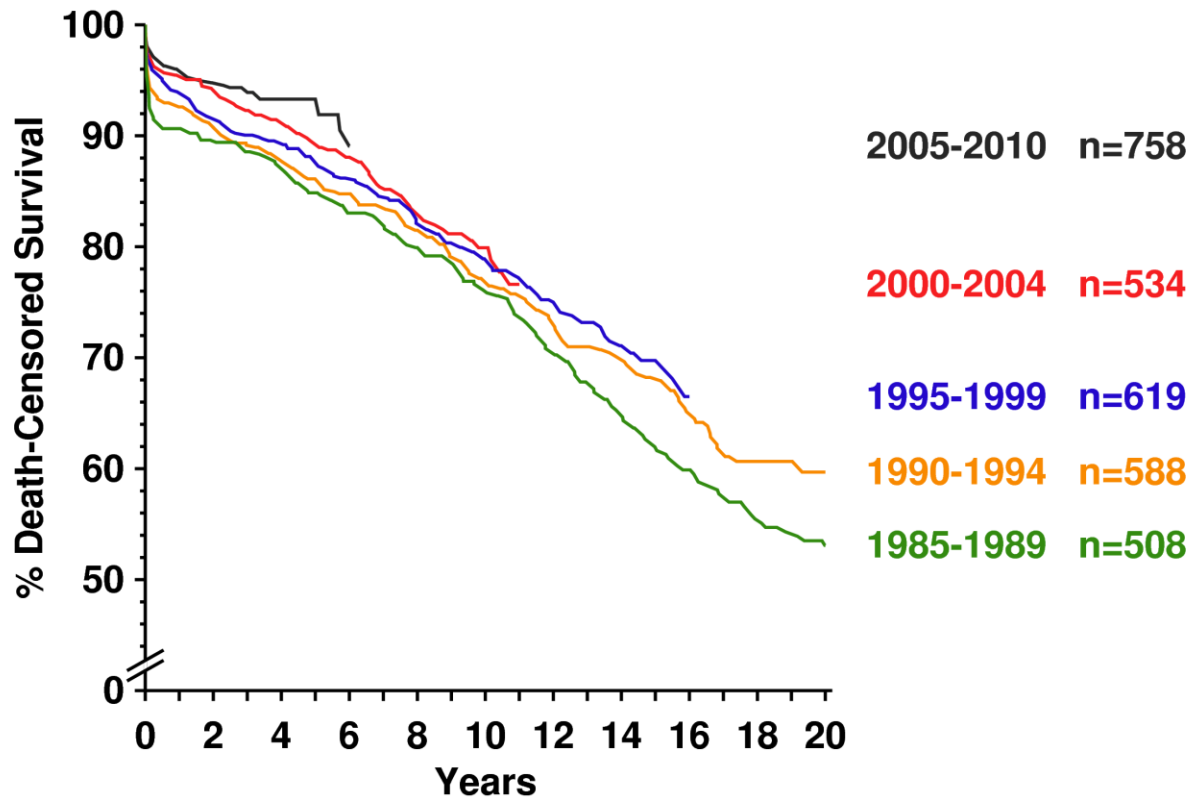
## **New Transplants**

**Regeneration & Organ Bioengineering : “Holey Grail”**

# Chronic Graft Loss



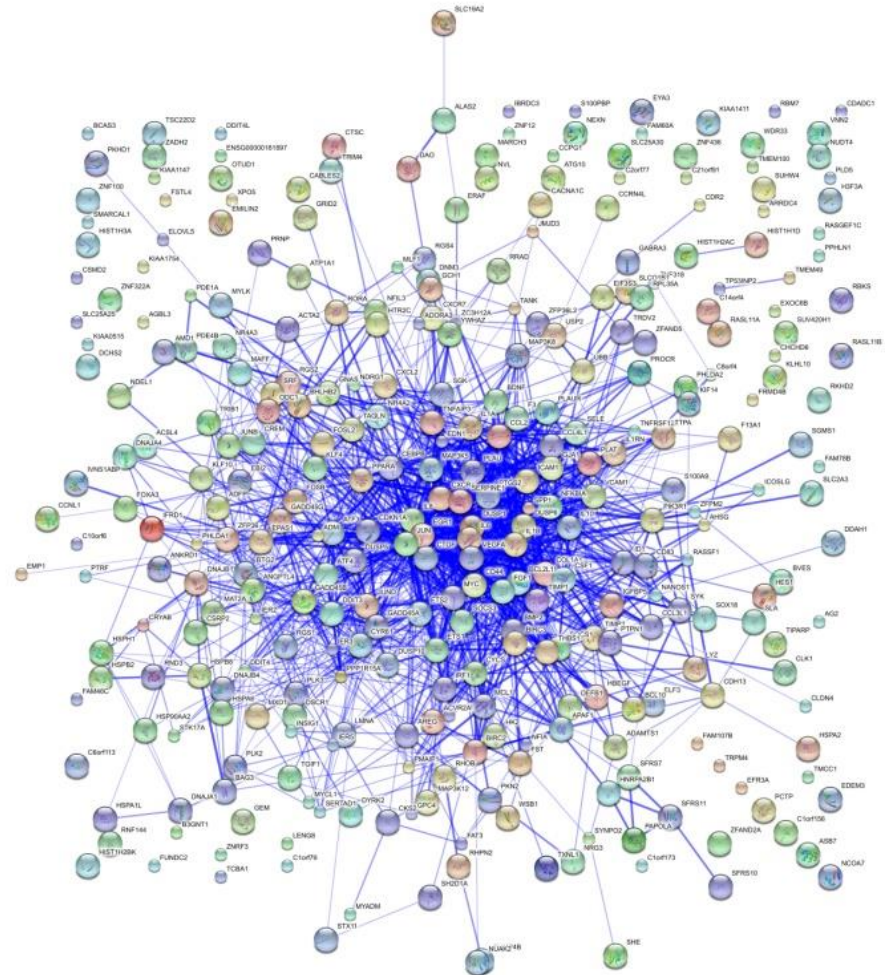
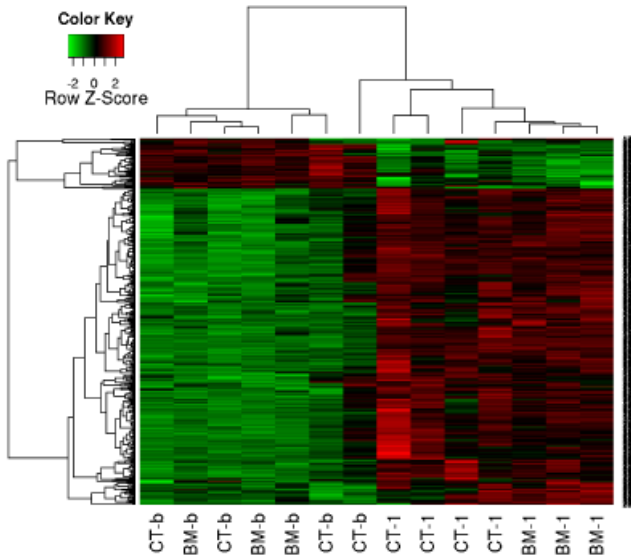
## KIDNEY TRANSPLANTATION: OUTCOME PER ERA



# Transcriptome $\longrightarrow$ Bioinformatics

*Genes actively expressed*  $\longrightarrow$  *Molecular Pathways Involved*

# $\longleftarrow$



*J van Liver Tx 2011*

*Naesens Nat Rev Nephrol 2010, Grigoryev JASN 2008, Akalin ISN 2010, Kotsch Tx 2010, Godwin PNAS 2010, Korbely Tx Int 2010*

# Minimizing Anti-Rejection Drugs



## Why?

- Infection & Cancer
- Toxicity
- Costs
- Compliance
- Quality of Life

# Minimization of anti-rejection drugs currently based on “trial and error”

BIO-DrIM



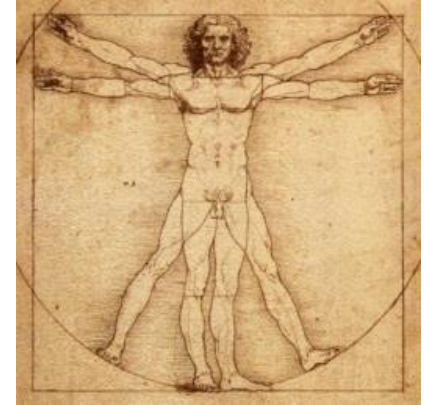
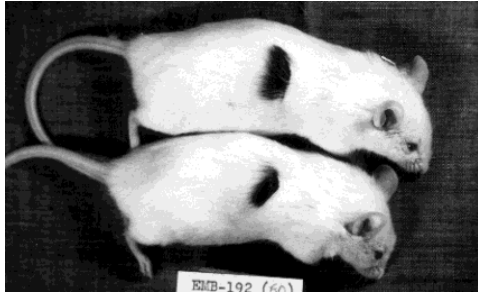
BIO-DrIM

**Personalised minimisation of immunosuppression after solid organ transplantation by biomarker-driven stratification of patients to improve long-term outcome and health-economic data of transplantation**

- Kidney + Liver
- Coordinator: Petra Reinke, Charité, Berlin
- EU contribution: €6 million
- Follow-on from FP5 (Indices of tolerance) and (FP6) Riset projects



# Completely Avoiding Anti-Rejection Drugs “Tolerance”



Peter Medawar

**How?**

**Co-Tx of donor  
immune cells**

**Problems?**

**Toxicity of preconditioning regimens**

Sykes, Sachs, Cosimi, Ildstad, others - Harvard, Columbia, Chicago



# The One Study

## A unified approach to evaluating cellular immunotherapy in solid organ transplantation

- Cell product technology (Treg, Tr1, Mreg, DC)
- One clinical trial - kidney
- Coordinator: Ed Geissler, Univ Regensburg
- EU contribution: €10.8 million
- [www.onestudy.org](http://www.onestudy.org)

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# Multi-Organ Disease: Multi-Organ Transplants



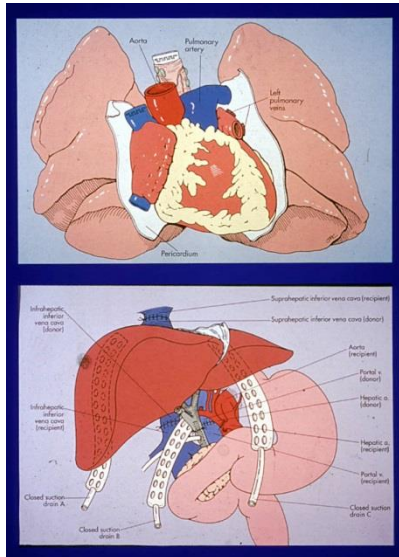
**Liver + Kidney**



**Liver + Pancreas**



**Liver + Bowel**

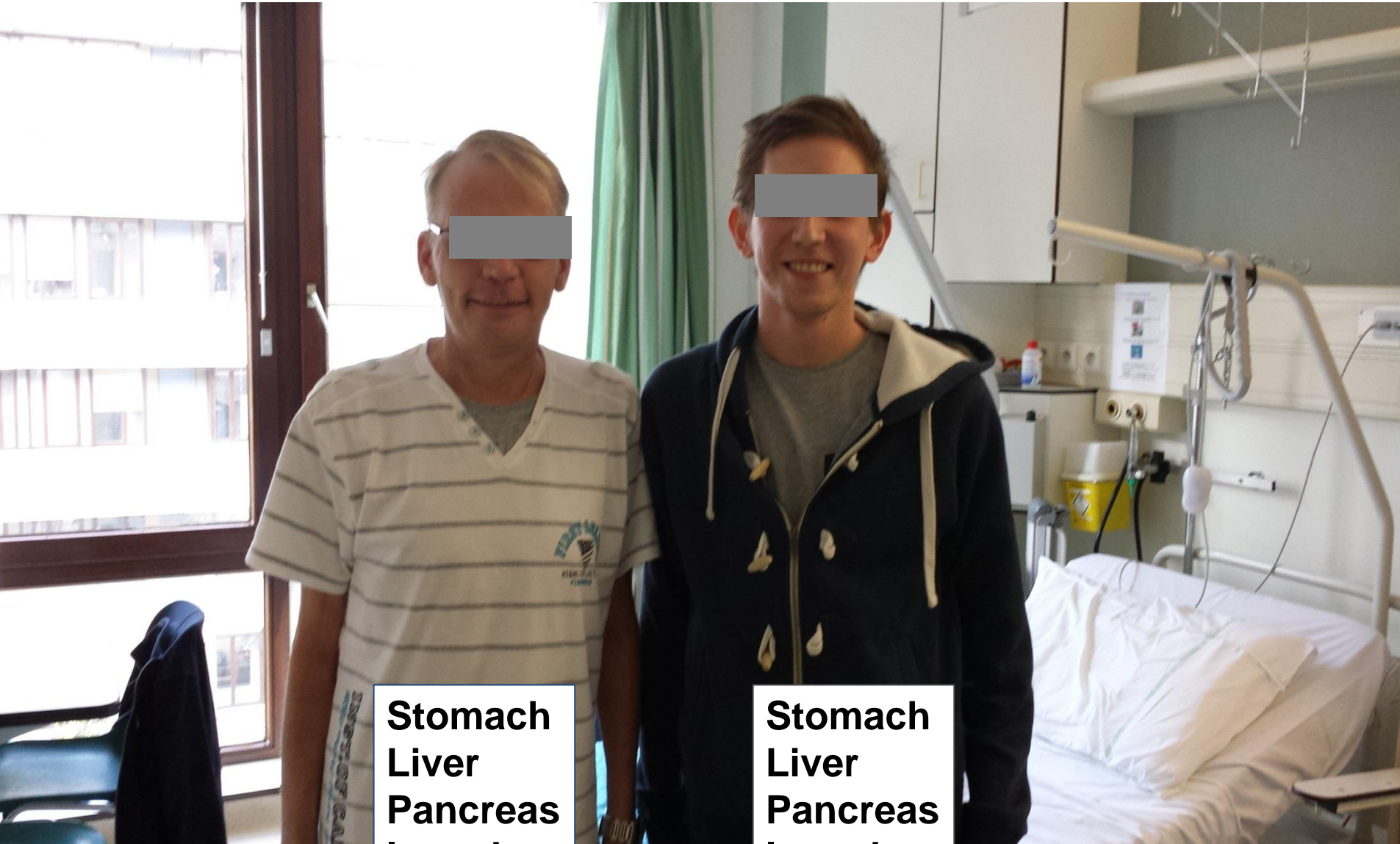


**Liver + Heart**

**Liver + Lung**

**Liver + Heart + Lung**

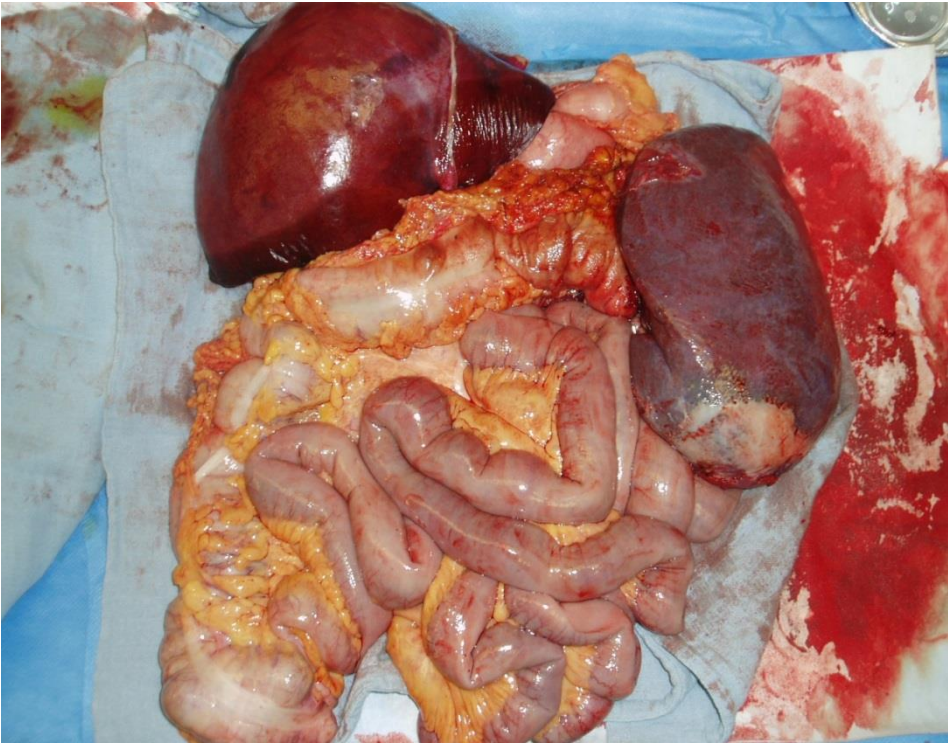
## 2 patients: 9 organs



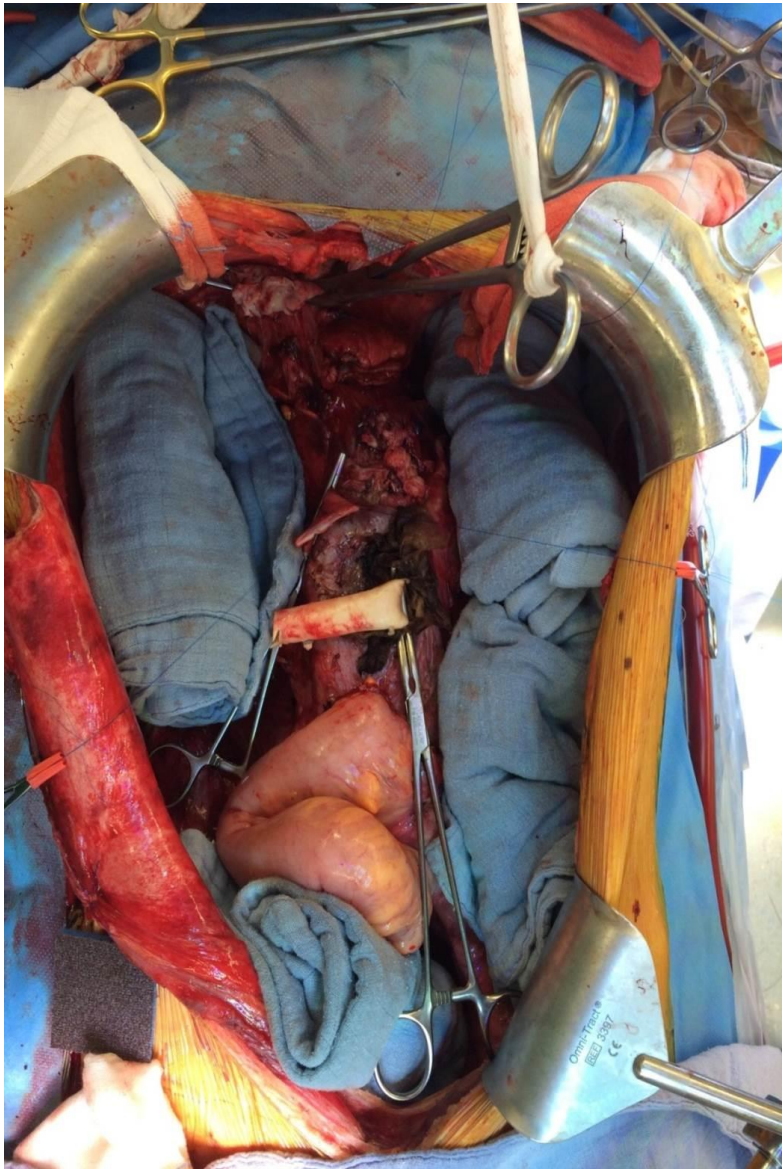
**Stomach  
Liver  
Pancreas  
Intestine  
Kidney**

**Stomach  
Liver  
Pancreas  
Intestine**

# Multivisceral transplantation

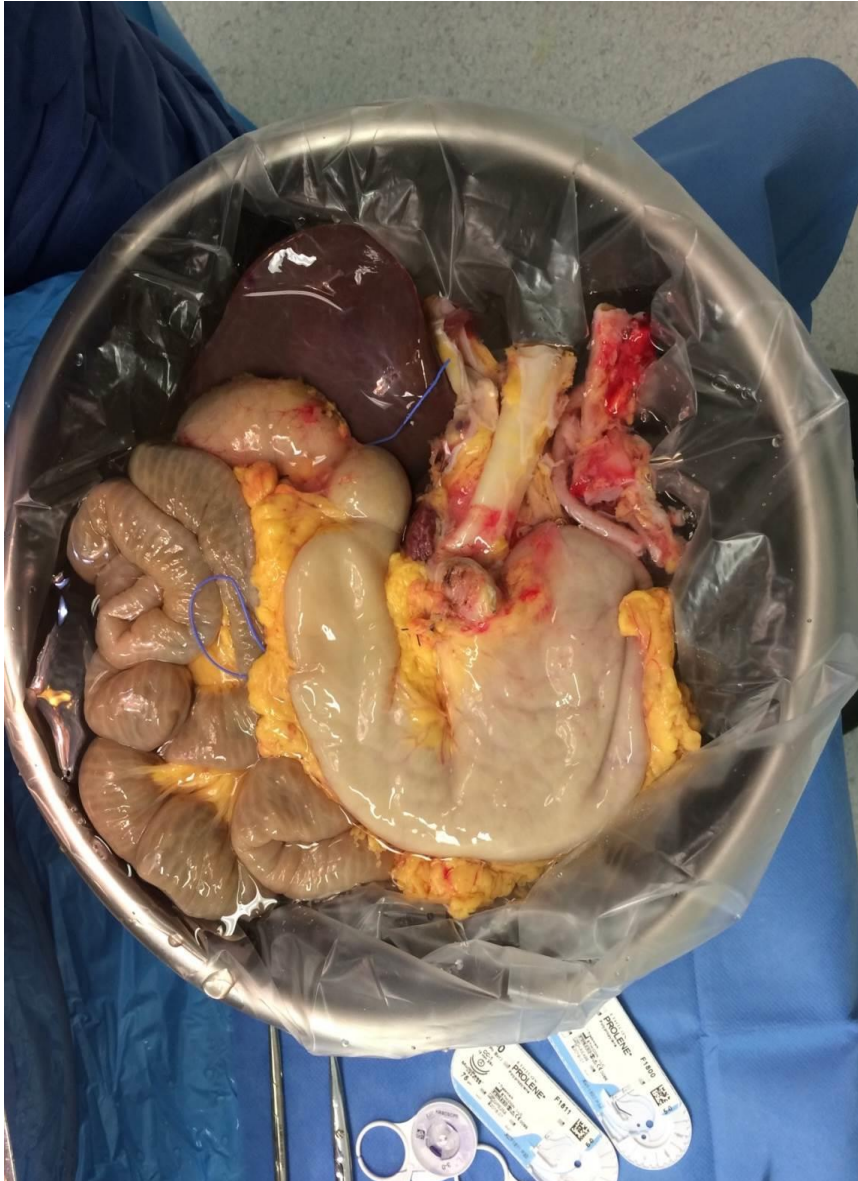


**Resected disease abdomen**

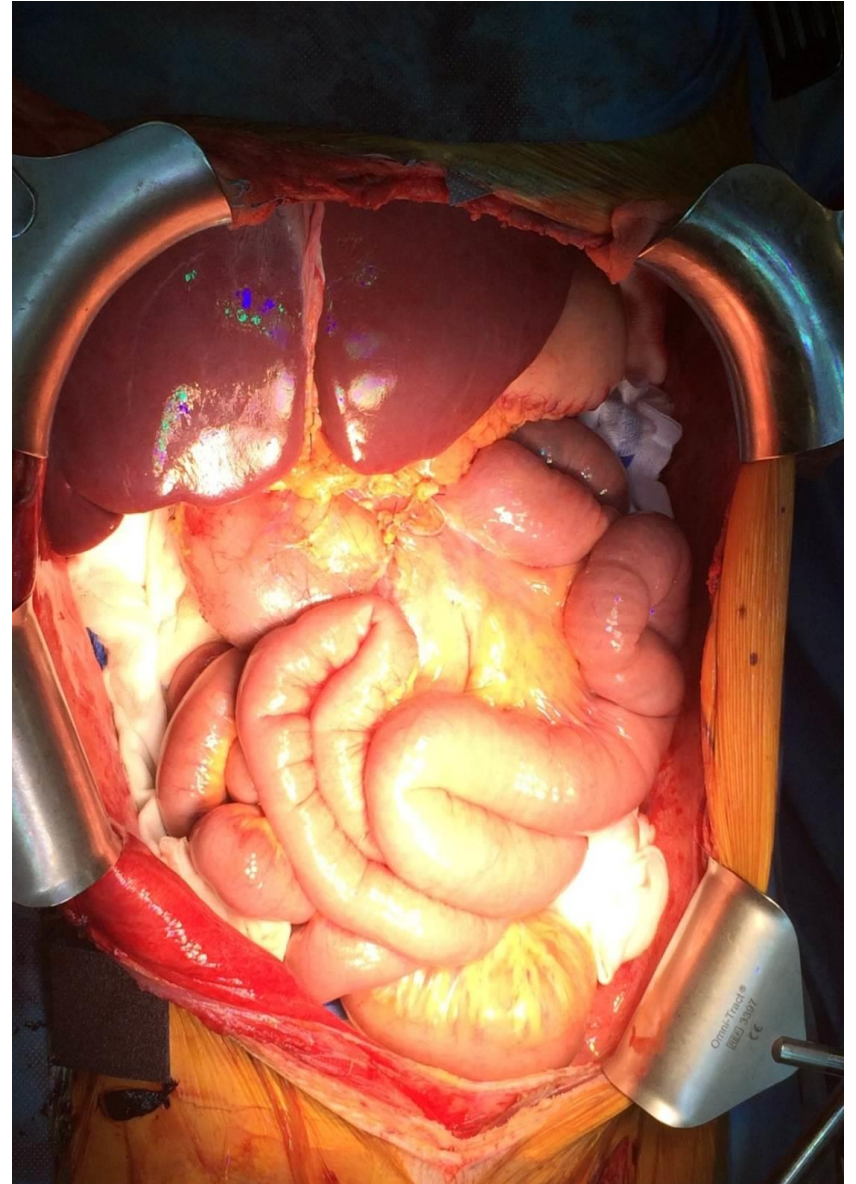


**Empty abdomen**

# Multivisceral transplantation



**New abdominal graft**



**Reperfused "new" abdomen**

## Livebirth after uterus transplantation

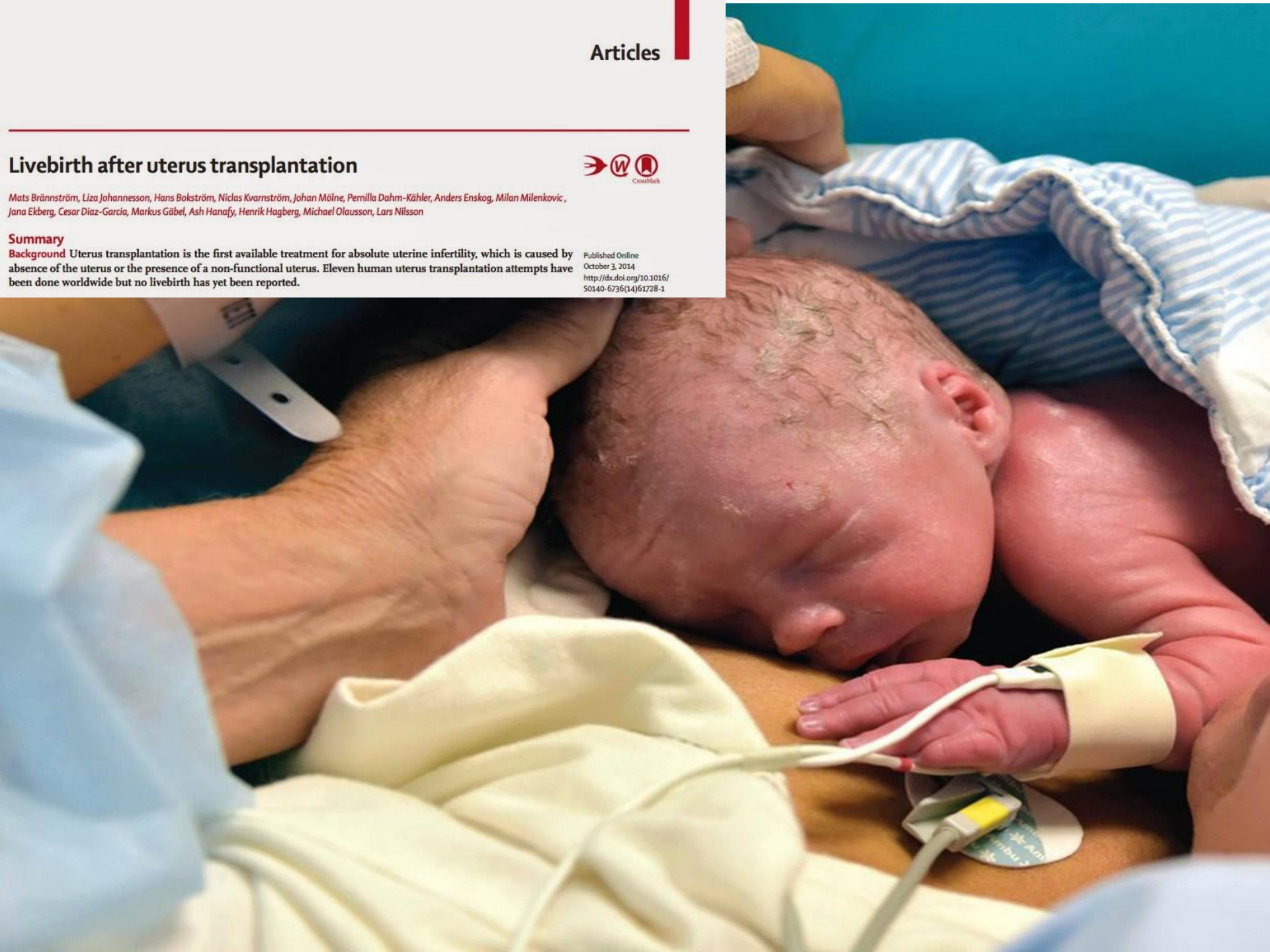
Mats Brännström, Liza Johannesson, Hans Bokström, Niclas Kvarnström, Johan Mölne, Pernilla Dahm-Kähler, Anders Enskog, Milan Milenkovic, Jana Ekberg, Cesar Diaz-Garcia, Markus Gäbel, Ash Hanafy, Henrik Hagberg, Michael Olausson, Lars Nilsson

### Summary

**Background** Uterus transplantation is the first available treatment for absolute uterine infertility, which is caused by absence of the uterus or the presence of a non-functional uterus. Eleven human uterus transplantation attempts have been done worldwide but no livebirth has yet been reported.



Published Online  
October 3, 2014  
[http://dx.doi.org/10.1016/S0140-6736\(14\)61728-1](http://dx.doi.org/10.1016/S0140-6736(14)61728-1)





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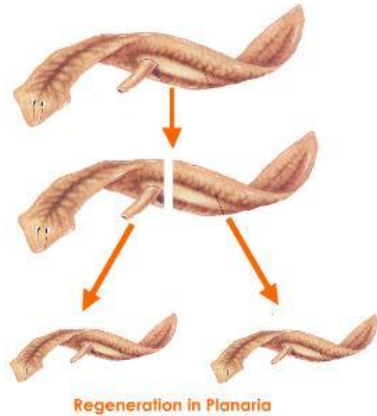
Toxicity: Minimize & Avoid Anti-Rejection Drugs

## **New Transplants**

# **Regeneration & Organ Bioengineering : “Holey Grail”**

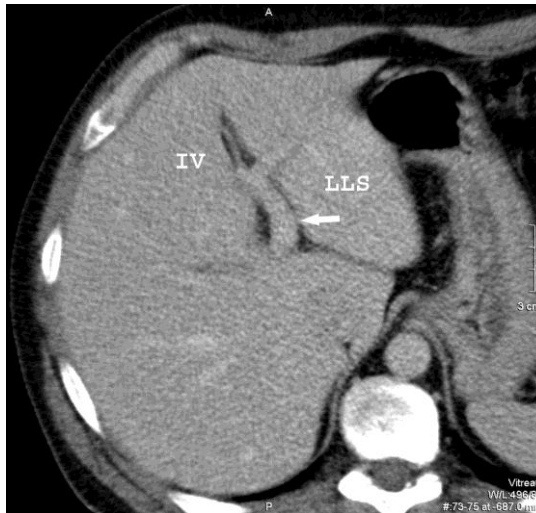
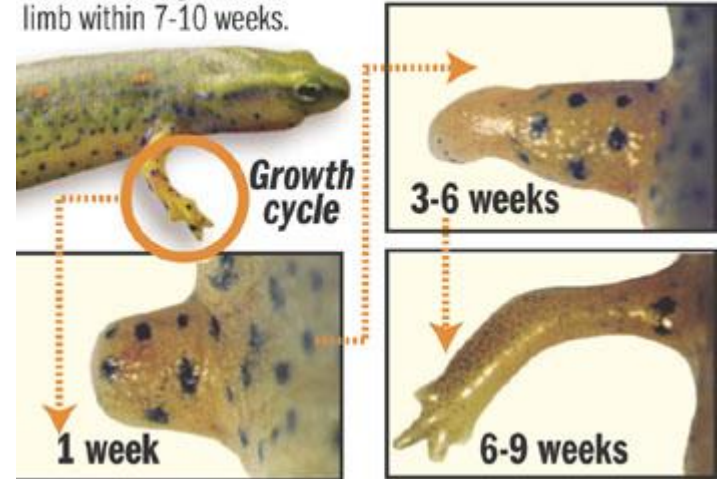
# Regeneration to cure organ failure?

Each piece of a planaria regenerates in a complete organism



## Regenerating a limb

A newt can regenerate an entire limb within 7-10 weeks.

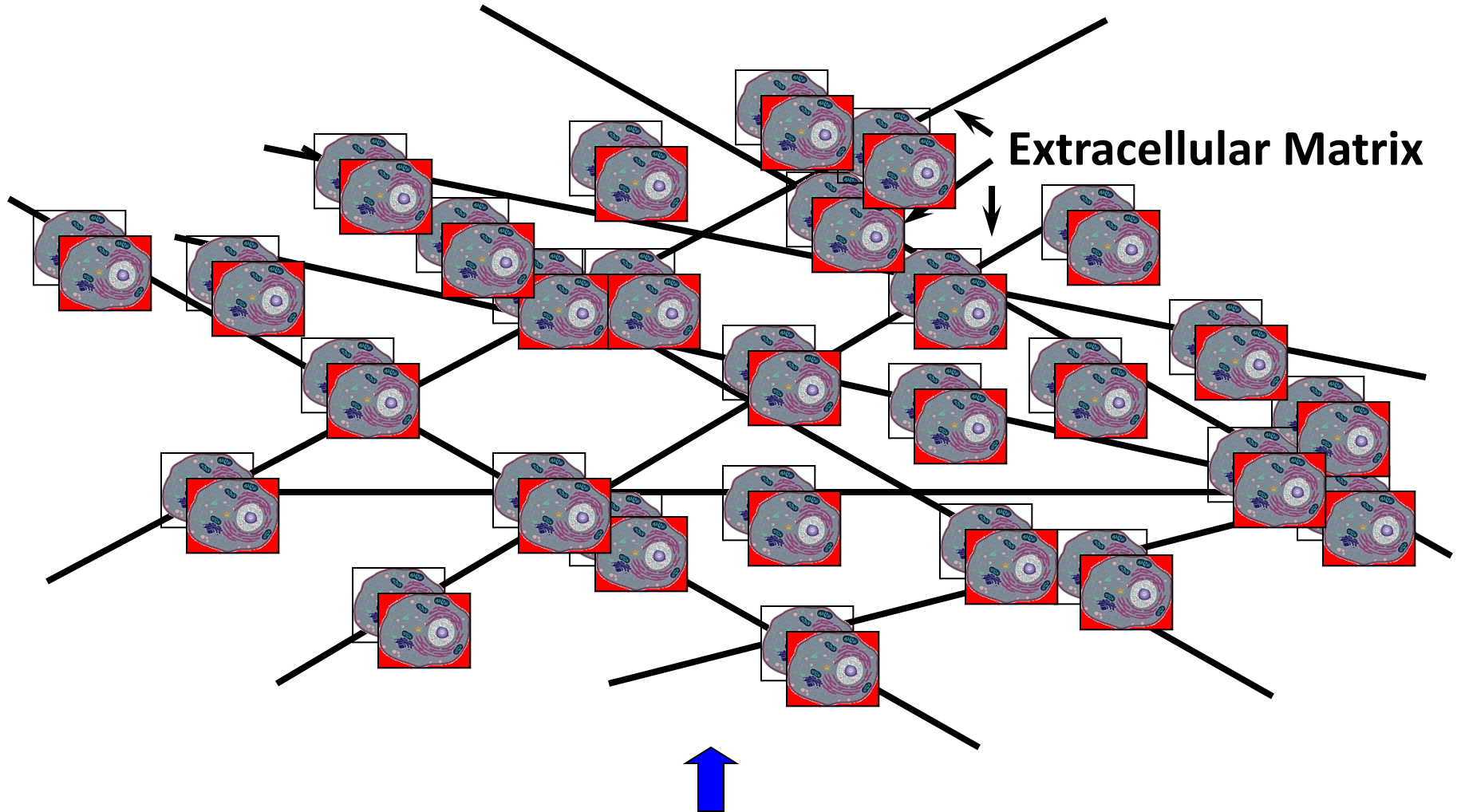


Liver regeneration  
after  
right lobe donation

Adult and Embryonal  
stem Cell Research

# Bioengineering to construct organs?

Organ = Matrix + Cells

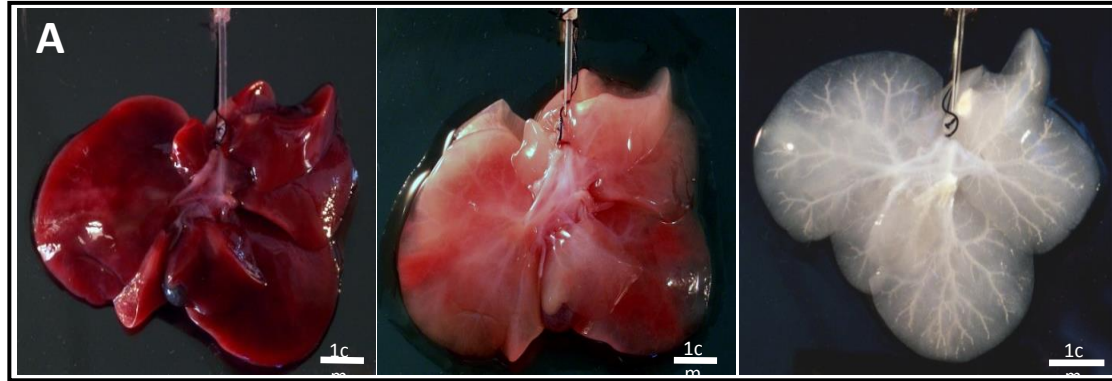


Extracellular Matrix

Triton X-100 + NH<sub>4</sub>OH

*Orlando G Organ bioengineering regeneration : new holy grail of transplantation ANN SURG, 2013*

# Construction of solid vascularized organ



**Decellularization**



**Scaffold**

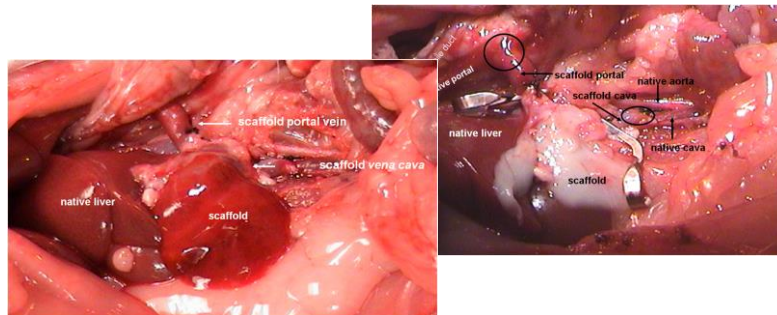


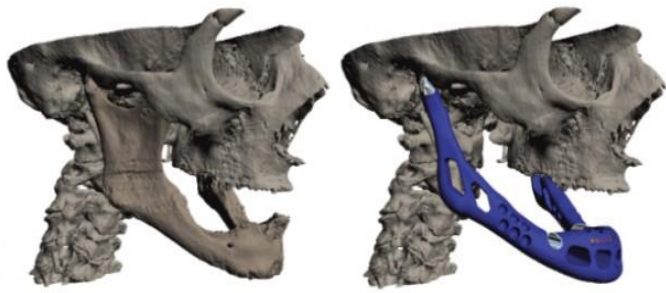
**Transplantation**



**Recellularization**

**Liver Progenitor & Endothelial cells**





Simple Scaffold



2014 - Medical First:  
3-D Printed Skull Successfully  
Implanted in Woman NBC News



Complex Scaffold



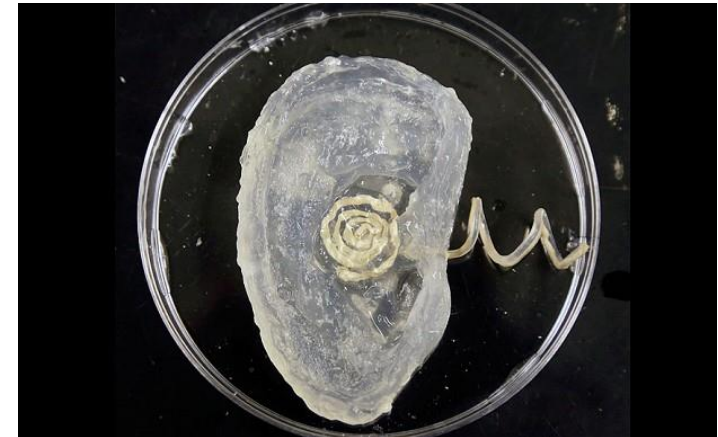
Scaffold + cellular “printing”

Scaffold + cellular “printing” +  
electronic

Nano Letter 2013; Manno; Princeton University

## 3D Printing

*3D printed bionic ear*



# Conclusions

- **Xenotransplants faced with biological obstacles**
- **Artificial organs bridge to transplant**
- **Maximize deceased donor pool: Legislation, detection, extension of criteria & public awareness**
- **Preservation: From “Ice box” to warm oxygenated perfusion**
- **Information on living donation**
- **Multi-organ & composite transplants increasingly performed**
- **Chronic graft loss: predictors, mechanisms and prevention**
- **Patient tailored minimization of anti-rejection drugs**
- **Tolerance (complete drug avoidance) achieved but not yet routinely**
- **Regeneration technologies may cure/prevent organ failure**
- **Organ bioengineering may allow construction of new tissues/organs (eliminating waiting list) with own recipient cells (eliminating rejection)**

# Transplant recipients summit kilimanjaro 5895m



February 2003  
Leuven Tx center



October 2014  
Groningen Tx center

# **TAKE HOME MESSAGE**

- **Transplantation: victim of its own success**
- **“Unfinished product”**
- **Organ shortage**
- **Dependence upon drugs**
- **Quick Progress**
- **Need for continued Research**